ANTI STREPTOKINASE ANTIBODIES AND RESPONSE TO THROMBOLYSIS WITH STREPTOKINASE IN ST SEGMENT ELEVATION MYOCARDIAL INFARCTION

A DISSERTATION SUBMITTED IN PART FULFILLMENT OF THE REQUIREMENTS FOR DM (BRANCH II, CARDIOLOGY) EXAMINATION OF THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI TO BE HELD IN JULY/AUGUST 2010

CERTIFICATE

This is to certify that this dissertation entitled **'Anti streptokinase antibodies and response to thrombolysis with streptokinase in ST segment elevation myocardial infarction'** is a bonafide work done by Dr. M S K Subhendu in partial fulfillment of rules and regulations for DM (Branch II- Cardiology) examination of the Tamil Nadu Dr. M.G.R. Medical University, to be held in July/August 2010.

Guide

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Dr. Oommen K George
MD, DM
Professor,
Department of Cardiology
Christian Medical College, Vellore

CERTIFICATE

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Head of the Department

_____

Dr. Sunil Thomas Chandy
MD, DM, FCSI, FIC (Aus)
Professor & Head
Department of Cardiology
Christian Medical College, Vellore

DECLARATION

I, Dr. M S K Subhendu, hereby declare that this dissertation entitled 'Anti streptokinase antibodies and response to thrombolysis with streptokinase in ST segment elevation myocardial infarction' has been prepared by me under the direct supervision and guidance of Dr. Oommen K George MD, DM, Professor, Department of Cardiology, Christian Medical College, Vellore. This is being submitted to Dr M.G.R medical university in partial fulfillment of regulations for the DM (Cardiology) examination to be held in July/August 2010.

This dissertation has not been submitted by me either in part or in full on any previous occasion to any university or institution for the award of any degree or diploma.

Place: Vellore
Date:

Dr. M S K Subhendu
Postgraduate student
Department of Cardiology
Christian Medical College
Vellore

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Dr. M S K Subhendu
Christian Medical College
Vellore

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INFARCTION

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Abstract

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Background : In India 60% of the patients with Acute Coronary Syndromes (ACS) present with ST segment elevation myocardial infarction (STEMI). Majority of these patients undergo thrombolysis with streptokinase (STK) for reperfusion. Studies have however shown that anti streptokinase (ASTK) antibodies in the serum neutralise the effect of STK. It has also been shown that the ASTK antibody titres are significantly elevated in the Indian population. We sought to assess the effect of ASTK antibodies on the efficacy of STK when used for reperfusion in patients with STEMI.

METHODS: Patients presenting to us with STEMI and planned to receive STK for reperfusion were enrolled in the study. Before initiation of thrombolysis, 3-4 ml of blood sample was collected for estimation of ASTK antibody titres. The patients were divided into two groups, those with window period less than and more than 6 hours. The baseline data was collected and the clinical markers of reperfusion were recorded. All the patients were subsequently followed up for 30 days and any major adverse cardiac events (MACE), if present, were noted.

RESULTS: We enrolled a total of 148 patients of which 133 patients (90%) were males. The mean window period (WP) at presentation was 5hrs 45min. Patients presenting directly to our centre numbered 46 while 102 patients were referred

from elsewhere. The mean WP in patients presenting directly to our centre was 2hrs 48 min while in the other patients it was 7hrs 5min.There was significant effect of time on reperfusion in both patients having low (P<0.001) and high (P=0.006) titres. There was also a significant effect of presence of ASTK antibodies. Patients who responded to thrombolysis were more likely to have low titres while those who did not respond had high ASTK antibody titres. This pattern was seen in both patients presenting before a WP of 6 hrs (P<0.001) and those presenting after 6 hrs (P=0.007).

MACE was noted in 30 (21%) patients. Patients with MACE were more likely to have high baseline ASTK antibody titres than those without MACE (P=0.042). The effect of ASTK antibodies appeared to have been present in both patients presenting before 6hrs (P=0.067) and after 6hrs (P=0.27).

CONCLUSION: ASTK antibodies are widely prevalent in the general population in varying titres. They seem to significantly impair the thrombolytic effect of STK in patients with STEMI. Patients with low ASTK antibody titre are more likely to benefit from thrombolysis with STK. Also those who develop MACE within 30 days of the event are more likely to have high ASTK antibody titre. Thus the presence of high ASTK antibody titres act as a poor prognostic marker in patients with STEMI undergoing thrombolysis with STK.

INTRODUCTION

Ischemic heart disease is the most common cause of death in both the developing and the developed countries[1]. By 2020 these diseases are expected to increase by more than 120% in the developing countries, compared to 30-60% in the developed countries[2]. 60% of the world's heart disease is expected to occur in India[3]. This brings a huge challenge to the healthcare system which is already inadequate and over stretched. Providing them the optimal care in the Indian settings will need more concrete data applicable to the general population. More studies need to be conducted in the local population as the findings of studies conducted in the western population may not be directly applicable to the Indian population.

Ischemic heart disease (IHD) continues to be the leading cause of death in the developed countries, but the spectrum appears to be different from that of the Indian population. Fewer than 40% of the patients with acute coronary syndromes (ACS) present with ST segment elevation myocardial infarction (STEMI) in the developed countries[4,5]. This is also showing a decreasing trend with time. On the other hand 60% of patients with ACS present with STEMI in India[6]. This suggests that patients with ACS are likely to have a worse prognosis in India than in the western countries. Appropriate management of STEMI is very important to decrease mortality as well as long term morbidity.

The most important management in the patients with STEMI, other than the usual drugs, is an early reperfusion therapy[7]. The different modes available for reperfusion presently is by either a fibrinolytic agent or primary percutaneous transluminal coronary angioplasty (PTCA). Fibrinolysis when introduced was a major breakthrough in coronary care and showed an 18% relative risk reduction in mortality at 30 days[8]. Subsequent introduction of primary PTCA showed further reduction in mortality compared to thrombolysis[9]. This has established primary PTCA as the treatment of choice for STEMI provided it is done in the set time limit as described[7]. However primary PTCA needs a larger set up and expertise which is still not widely available. In India only around 8% of the patients undergo PTCA while more than 50% of the patients undergo thrombolysis[6]. There are many thrombolytic agents available now with the fibrin selective agents showing better results than the non selective agent streptokinase[10]. However because of the high costs associated with the fibrin specific agents, streptokinase continues to be the most commonly used thrombolytic agent in the developing countries.

Streptokinase (STK) is an extracellular non-enzymatic protein produced by various strains of beta haemolytic streptococci. However, a disadvantage to its use is its antigenicity due to the widespread presence of antibodies in the population, presumed secondary to previous streptococcal exposure or infection. A measurable level of antibodies to STK is nearly omnipresent in the population as a consequence of the high frequency of streptococcal infection[11]. Presence of high levels of anti streptokinase (ASTK) antibodies are likely to inhibit the

fibrinolytic activity. Clinical failure of the activation of the fibrinolytic system by STK has been reported due to the presence of a high titre of ASTK antibodies[12]. This could be especially problematic in populations with high endemic streptococcal infections where the ASTK antibody titres are much higher than those in the western countries[13]. The antibody titres are similarly very high in the Indian population too[14]. Under these circumstances the benefit of STK can not be guaranteed in the general population.

Studies have been done to evaluate the effect of ASTK antibodies on the outcome of thrombolysis. These studies have shown a varying picture with some reporting no effect on the outcome of thrombolysis[15,16] and some suggesting a failure of thrombolysis due to high antibody titres[17,18,19]. However, most of these studies were carried out without having taken the window period into account and only the markers of reperfusion were assessed.

Most of the patients in India receive thrombolytic therapy as the mode of reperfusion. This is mainly because the patients have to pay themselves for their treatment and can not afford the costlier option of primary percutaneous transluminal coronary angioplasty (PTCA)[6]. While this being one factor, another factor could also be that most of the patients are seen initially at a centre without facilities for primary PTCA and thrombolysed with STK to avoid a delay in shifting to a higher centre. However, in view of the possibility of failure of STK as the thrombolytic agent, it may be prudent to tailor the therapy in individual cases.

This needs careful consideration given the fact that the benefit of primary PTCA continues to be similar even upto 12 hours of presentation. This optimization could be in the form of emphasizing the need to use the newer fibrin specific agents which are not affected by the presence of the ASTK antibodies or allowing a longer door to balloon period for primary PTCA especially in those patients who have longer window periods at presentation and are also likely to have high ASTK antibody titres.

This study was planned to assess the outcome of thrombolysis in patients thrombolysed with STK and effect of presence of ASTK antibodies in the serum. It was planned to assess the immediate reperfusion based on clinical criteria and also to look for clinical end points of rest angina, reinfarction, heart failure and death at 30 days and to see if it is affected in anyway by the presence of ASTK antibodies.

AIMS AND OBJECTIVES

1. To assess the clinical criteria for reperfusion in patients with STEMI who were thrombolysed with streptokinase.

2. To follow up these patients for 30 days and look for any major adverse cardiac event namely rest angina, reinfarction, heart failure or death.

3. To estimate the anti streptokinase antibody titres in these patients in a serum sample collected prior to them receiving streptokinase

4. To assess any correlation between the antibody titres and successful thrombolysis or the major adverse cardiovascular events.

REVIEW OF LITERATURE

Epidemiology

Cardiovascular disease (CVD) is a major cause of disability and premature death throughout the world, and contributes substantially to the escalating costs of health care. The underlying pathology is atherosclerosis, which develops over many years and is usually advanced by the time symptoms occur, generally in middle age. Acute coronary and cerebrovascular events frequently occur suddenly, and are often fatal before medical care can be given.

Of an estimated 58 million deaths globally from all causes in 2005, cardiovascular disease accounted for 30%. This proportion is equal to that due to infectious diseases, nutritional deficiencies, and maternal and perinatal conditions combined[20]. It is important to recognize that a substantial proportion of these deaths (46%) were of people under 70 years of age, in the more productive period of life[21].

CVDs are no longer confined by geographical area or by age, sex, or socioeconomic boundaries. Heart disease has already reached epidemic proportions in poorer countries. Except in Africa, noncommunicable diseases outnumbered communicable diseases in all WHO regions worldwide. In Southeast Asia alone, 7 423 000 deaths were due to noncommunicable diseases as compared with 5 730 000 deaths related to communicable diseases in the

year 2002. Globally, ischemic heart disease (IHD) was the leading killer in the age group ≥60 years, and, with 1332000 deaths in adults aged 15–59 years, IHD was ranked behind HIV/AIDS only[22].

It is to be noted however that the principal cardiovascular disorder responsible for the global rise in mortality is no longer rheumatic heart disease, but rather atherosclerotic vascular disease. Ischemic heart disease is the leading cause of death in the world, and cerebrovascular disease is the second leading cause[23,24]. Cardiovascular diseases are responsible for 30% of all deaths worldwide each year[23,24]. It is often assumed that atherosclerosis is a disease of affluent, industrialized countries. However, 80% of these deaths occur in low-to-middle income countries of varying size like China, Russia, Poland, Mauritius, Argentina, and India[23].

Cardiovascular disease in India

India is in the midst of a demographic transition. The average life expectancy at birth in India is 63.7 years, being 63.1 for males and 64.4 for females, compared with the national average of 41.2 years in 1951–1961[22]. There has been a decline in death rate from 1941 to 1971, followed by a sharp decline in birth rate from 1971 onwards. This rise in life expectancy in India is attributed to a decrease in infectious, parasitic, and nutritional disorders and, in itself, is a remarkable achievement. However, this demographic transition has also led to an increase in the number of older people (aged ≥60 years), from 19.61 million in

1950 to 75.93 million in 2000. The increase in life expectancy has brought a large section of the population to an age where CVD starts manifesting itself. In India, coronary artery disease (CAD) rates have increased during the last 30 years, whereas declining trends have been noticed in the developed Western countries[22].

Reports on CAD in Indians from different parts of the world have shown that Indians are at 3–4 times higher risk of CAD than white Americans, 6 times higher than Chinese, and 20 times higher than Japanese[25,26,27]. The exact prevalence of CAD in India is difficult to estimate owing to the lack of a large prospective study. Absence of a centralized death registry for CVDs and irregularities in completion of death certificates also hamper estimation of the actual burden of CVD.

Heart diseases are occurring in Indians 5 to 10 years earlier than in other populations around the world[28,29]. According to the INTERHEART study, the median age for first presentation of acute MI in the South Asian (Bangladesh, India, Nepal, Pakistan, Sri Lanka) population is 53 years, whereas that in Western Europe, China, and Hong Kong is 63 years, with more men than women affected[30].

The first myocardial infarction (MI) occurs in 4.4% of Asian women and 9.7% of men at age less than 40 years, which is 2 to 3.5 fold higher than in the West European population and is third highest of all the regions studied worldwide[30].

The INTERHEART study[30], involving 52 countries, established an association between conventional modifiable risk factors for MI in all regions of the world, including South Asia, and in both sexes and at all ages. In South Asians, apolipoprotein (Apo) B/ApoA1 and smoking were the important risk factors, as in the rest of the world. However, hypertension, abdominal obesity, and diabetes had more severe effects in South Asia. The study also showed that hypertension and diabetes were more important risk factors in younger Indian women than men. It was also observed that the risk of CAD increased incrementally with smoking and it was a greater risk factor in younger men than in women.

It has also been shown that the majority of MI risk in native South Asians can be explained by 9 potentially modifiable risk factors with similar collective impact as in other countries[31]. These are –

- Apolipoprotein B100/apolipoprotein A-I ratio
- Current and former smoking
- Hypertension
- Diabetes
- High waist-to-hip ratio
- Psychosocial factors (stress or depression)
- Moderate- or high-intensity exercise
- Alcohol consumption
- Consumption of fruits and vegetables

South Asians had a lower age at presentation of first MI. The younger age of first MI among the South Asian cases is largely because of the higher prevalence of risk factors in native South Asians.

The 4 main risk factors, which showed consistently significant associations across all South Asian countries in both sexes were current and former smoking, high ApoB100/Apo-I ratio, history of hypertension, and history of diabetes.

The 9 risk factors collectively explained 86.0% of the risk in South Asians and suggested that modifying behavior related to known risk factors could lead to a substantial impact[31].

Between 1990 and 2020, ischemic heart diseases are expected to increase by 120% for women and 137% for men in developing countries, compared with 30-60% in developed countries[2]. By 2010, 60% of the world's heart disease is expected to occur in India[3]. In addition, the proportion of patients with STEMI at 60% of the acute coronary syndrome patients is much higher than the proportion observed in developed countries where fewer than 40% had STEMI[5]. This suggests that the patients with acute coronary syndromes in India are likely to have a worse prognosis than the patients in western countries. Also the average age of ACS in India at 57 years is also much lower than that in western countries. They also take longer time to reach hospitals, and longer time to initiation of treatment. The majority of patients receive thrombolytic therapy as the means for

reperfusion with only 8% of STEMI patients being treated with primary PTCA. Correspondingly the 30 days mortality rate in Indian patients with ACS is higher than in registries in high income countries[6].

Myocardial Infarction

Myocardial infarction is defined by pathology as myocardial cell death due to prolonged ischemia. Cell death is categorized pathologically as coagulation and/or contraction band necrosis, which usually evolves through oncosis, but can result to a lesser degree from apoptosis[32].

After the onset of myocardial ischemia, cell death is not immediate but takes a finite period to develop (as little as 20 min or less in some animal models). It takes several hours before myocardial necrosis can be identified by macroscopic or microscopic post-mortem examination. Complete necrosis of all myocardial cells at risk requires at least 2–4 h or longer depending on the presence of collateral circulation to the ischemic zone, persistent or intermittent coronary arterial occlusion, the sensitivity of the myocytes to ischemia, preconditioning, and/or, finally, individual demand for myocardial oxygen and nutrients.

Myocardial infarction is generally the result of acute rupture or ulceration of an atherosclerotic plaque situated within a major epicardial coronary artery. Exposure of the intimal layer initiates a cascade of platelet activation and

thrombosis resulting in occlusion of the vessel and infarction of the subjacent myocardium[32].

Myocardial infarctions are usually classified by size: microscopic (focal necrosis), small (<10% of the LV myocardium), moderate (10–30% of the LV myocardium), and large (>30% of the LV myocardium), and by location[32].

Definition of myocardial infarction

Myocardial infarction can be defined pathologically as acute, healing, or healed. Acute myocardial infarction is characterized by the presence of polymorphonuclear leukocytes. If the time interval between the onset of the infarction and death is quite brief, e.g. 6 h, minimal or no polymorphonuclear leukocytes may be seen. The presence of mononuclear cells and fibroblasts, and the absence of polymorphonuclear leukocytes characterize healing infarction. Healed infarction is manifested as scar tissue without cellular infiltration. The entire process leading to a healed infarction usually takes at least 5–6 weeks. Reperfusion may alter the macroscopic and microscopic appearance of the necrotic zone by producing myocytes with contraction bands and large quantities of extravasated erythrocytes. Myocardial infarctions can be classified temporally from clinical and other features, as well as according to the pathological appearance, as evolving (<6 h), acute (6 h–7 days), healing (7–28 days), and healed (29 days and beyond)[32].

Criteria for acute myocardial infarction

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following
  - Symptoms of ischaemia;
  - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)];
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3x99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomakers greater than 5x99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.
- Pathological findings of an acute myocardial infarction.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a healed or healing myocardial infarction.

ECG abnormalities of myocardial ischemia or infarction may be inscribed in the PR segment, the QRS complex, and the ST segment or T-waves. The earliest manifestations of myocardial ischemia are typical T-waves and ST segment changes[33]. Increased hyper-acute T-wave amplitude with prominent symmetrical T-waves in at least two contiguous leads is an early sign that may precede the elevation of the ST segment. Increased R-wave amplitude and width (giant R-wave with S-wave diminution) are often seen in leads exhibiting ST elevation, and tall T-waves reflecting conduction delay in the ischemic myocardium[34]. Transient Q-waves may be observed during an episode of acute ischemia or rarely during acute myocardial infarction with successful reperfusion[35].

The J-point is used to determine the magnitude of the ST elevation. J-point elevation in men decreases with increasing age; however, that is not observed in women, in whom J-point elevation is less than in men[36].

Contiguous leads means lead groups such as anterior leads (V1-V6), inferior leads (II, III, and aVF), or lateral/apical leads (I and aVL). Supplemental leads such as V3R and V4R reflect the free wall of the right ventricle.

Although the criteria require that the ST shift be present in two or more contiguous leads, occasionally acute myocardial ischemia may create sufficient ST segment shift to meet the criteria in one lead but have slightly less than the required ST shift in an adjacent contiguous lead. Lesser degrees of ST

displacement or T-wave inversion in leads without prominent R-wave amplitude do not exclude acute myocardial ischemia or evolving myocardial infarction.

Reperfusion strategy in myocardial infarction

Although rapid spontaneous reperfusion of the infarct artery may occur, in the majority of patients there is persistent occlusion of the infarct artery in the first 6 to 12 hours while the affected myocardial zone is undergoing necrosis. Prompt and complete restoration of flow in the infarct artery can be achieved by pharmacological means (fibrinolysis), percutaneous coronary intervention (PCI) [balloon angioplasty with or without deployment of an intracoronary stent under the support of pharmacological measures to prevent thrombosis], or surgical measures. Evidence exists that expeditious restoration of flow in the obstructed infarct artery after the onset of symptoms in patients with STEMI is a key determinant of short- and long-term outcomes regardless of whether reperfusion is accomplished by fibrinolysis or PCI[37,38,39].

A critically important goal of reperfusion is to restore flow in the infarct artery as quickly and as completely as possible, but the ultimate goal of reperfusion in STEMI is to improve myocardial perfusion in the infarct zone. Despite adequate restoration of flow in the epicardial infarct artery, perfusion of the infarct zone may still be compromised by a combination of microvascular damage and reperfusion injury[40,41]. Microvascular damage occurs as a consequence of downstream embolization of platelet microemboli and thrombi followed by the

release of substances from activated platelets that promote occlusion or spasm in the microvasculature. Reperfusion injury results in cellular edema, free radical formation, calcium overload, and acceleration of the apoptotic process. Cytokine activation in the infarct zone leads to neutrophil accumulation and inflammatory mediators that contribute to tissue injury.

Time from onset of symptoms to fibrinolytic therapy is an important predictor of MI size and patient outcome[42]. The efficacy of fibrinolytic agents in lysing thrombus diminishes with the passage of time[43]. Fibrinolytic therapy administered within the first 2 hours (especially the first hour) can occasionally abort MI and dramatically reduces mortality[8,44]. Because the benefit of fibrinolytic therapy is directly related to the time from symptom onset, treatment benefit is maximized by the earliest possible application of therapy.

The present recommendations for fibrinolytic therapy say that:
In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and ST elevation greater than 0.1 mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads or patients with symptom onset within the prior 12 hours and new or presumably new LBBB.

In the absence of contraindications, it is reasonable to administer fibrinolytic therapy to STEMI patients with symptom onset within the prior 12 hours and 12-

lead ECG findings consistent with a true posterior MI. It is also reasonable to administer fibrinolytic therapy to patients with symptoms of STEMI beginning within the prior 12 to 24 hours who have continuing ischemic symptoms and ST elevation greater than 0.1 mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads[7].

Contraindications and Cautions for Fibrinolysis Use in ST-Elevation Myocardial Infarction[7]

Absolute contraindications

- Any prior ICH
- Known structural cerebral vascular lesion (eg, AVM)
- Known malignant intracranial neoplasm (primary or metastatic)
- Ischemic stroke within 3 months EXCEPT acute ischemic stroke within 3 hours
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed head or facial trauma within 3 months

Relative contraindications

- History of chronic severe, poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (SBP greater than 180 mm Hg or DBP greater than 110 mm Hg)†
- History of prior ischemic stroke greater than 3 months, dementia, or known intracranial pathology not covered in contraindications

- Traumatic or prolonged (greater than 10 minutes) CPR or major surgery (less than 3 weeks)
- Recent (within 2 to 4 weeks) internal bleeding
- Noncompressible vascular punctures
- For streptokinase/anistreplase: prior exposure (more than 5 days ago) or prior allergic reaction to these agents
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulants: the higher the INR, the higher the risk of bleeding

The constellation of clinical features that must be present to serve as an indication for fibrinolysis includes symptoms of myocardial ischemia and ST elevation fulfilling the criteria as mentioned, or new or presumably new LBBB on the presenting ECG[8,45]. In the very early phase of STEMI, giant hyperacute T waves may precede ST elevation[46]. True posterior MI may be manifested by tall R waves in the right precordial leads and ST-segment depression in leads V1 through V4, especially when T waves are upright. Repeat ECGs and incorporation of additional leads such as V7 through V9 are more specific for the detection of posterior infarction. Patients with LBBB or anterior ST elevation are at greater inherent risk from MI and achieve greater benefit with fibrinolytic therapy.

Efficacy of intravenous fibrinolytic therapy in STEMI

It has been well established that fibrinolytic therapy provides a survival benefit for patients with STEMI, based on large, well-controlled clinical trials[47,48,49]. The mechanisms of benefit, which may have different time dependencies, include salvage of myocardium with reduced infarct size, favourable effect on infarct healing and myocardial remodeling, and reduced electrical heterogeneity and potential for life-threatening ventricular arrhythmia[50].

An overview of the results of 9 trials by the Fibrinolytic Therapy Trialists' Collaborative Group comparing the outcomes of patients undergoing fibrinolytic therapy and those of controls demonstrated a highly significant 18% relative reduction in 35-day mortality (9.6% fibrinolysis versus 11.5% control), which corresponds to absolute reductions in 35-day mortality rates of approximately 30 per 1000 for patients who arrived at the hospital within 6 hours of the onset of symptoms and of approximately 20 per 1000 for patients who arrived 7 to 12 hours after the onset of symptoms[8]. This survival benefit is maintained over the long term (up to 10 years). Mortality reduction from fibrinolytic therapy is greatest within the first hour after symptom onset; thereafter, decline in benefit of approximately 1.6 lives per 1000 patients treated is seen per 1-hour delay.

Thrombolytic agents

The fibrinolytic agents currently approved for treating patients with STEMI include streptokinase, alteplase, reteplase, and tenecteplase . These agents are

commonly referred to as plasminogen activators, since their mode of action is through the conversion of the enzymatically inert plasminogen (PG) of the fibrinolytic system to an active protease, plasmin (PN), that dissolves the fibrin clots and solubilises degradation products, which can be removed by the phagocytes.

STREPTOKINASE

Streptokinase was the first available and most widely studied agent for thrombolysis. Streptokinase (STK) is an extracellular non-enzymatic protein produced by various strains of beta haemolytic streptococci. STK is a single-chain protein of molecular weight 47 kDa containing 414 amino acids, having isoelectric pH 4.7[51]. The enzyme has its maximum activity between pH 7.3 and 7.6. The capacity of STK to cause lysis of blood clots was first described by Tillet and Carner in 1933 and the effect was thought to be a direct enzymatic action on fibrin. Milstone in 1941 demonstrated that STK achieved its effect through activation of plasma protein. At first STK was called fibrinolysin, until it was found that it induced fibrinolysis indirectly through activation of a plasma protein in the fibrinolysis system in man. The term streptokinase was then coined by Christensen to describe the bacterial extract[52].

STK has no proteolytic activity of its own and thus activates PG to PN indirectly by first forming a high affinity equimolar complex with PG (STK–PG activator complex)[51]. It forms a 1:1 complex with plasminogen causing conversion to

plasmin. It is nonspecific, activating circulating as well as clot-bound plasminogen, and causes extensive fibrinogen depletion.

Streptokinase is antigenic. Neutralizing antibodies are significant following use, and repeat administration should be avoided. Allergic reaction (rash, chills, urticaria) occurs in around 4% of patients and anaphylactic shock occurs in 0.5% of patients[48]. Hypotension can be significant (average decrease ~ 35 mm systolic blood pressure (SBP)[53] and may be worsened by rapid administration, which excludes bolus use and necessitates constant IV infusion. It is commonly given as 1.5 million units over 60 min.

ALTEPLASE

Tissue type plasminogen activator (t-PA) is a naturally occurring serine protease, which is produced by healthy endothelium. Its levels are increased with exercise and inhibited by plasminogen activator inhibitor (PAI-1). Alteplase is a commercially available, genetically engineered, bacterially produced version of human t-PA. It exhibits marked specificity for the plasminogen-fibrin complex, although at the doses necessary to achieve rapid lysis, there is ~ 50% depletion of circulating fibrinogen. t-PA is associated with a higher early recanalization rate relative to streptokinase[54], but may be accompanied by an increase rate of reocclusion[55]. The half-life is approximately 5 min; thus, t-PA must be administered via continuous IV infusion over 90 min.

The accelerated dosing regimen has been proven to be the most effective[56]: 15 mg bolus over 1–2 min followed by 0.75 mg/kg IV (≤ 50mg) over 30 min followed by 0.5 mg/kg (≤ 35 mg) over 60 min.

Weight adjustment is recommended because of excessive bleeding in lighter weight (<60 kg) patients and a trend toward decreased lysis in heavy weight (>90 kg) individuals[57]. Higher dose and double-bolus regimens have been associated with unacceptable bleeding rates[58,59]. The accelerated or front-loaded dosing regimen has been shown to have higher early patency rates, similar safety profile[56], and lower incidences of reocclusion as compared with the standard dosing regimen[60].

The TIMI (Thrombolysis in Myocardial Infarction), phase 1 trial randomly assigned 290 patients with evolving acute MI to alteplase or to streptokinase. Alteplase was far superior in achieving coronary reperfusion; twice as many occluded infarct-related arteries opened after 90 minutes with alteplase than with streptokinase[61].

The GUSTO I study (41,021 patients) tested the accelerated dose regimen combined with intravenous heparin. Despite an increase in intracerebral bleeding with t-PA, overall benefit as assessed from the combined endpoint of total mortality and disabling stroke was significantly better with t-PA as compared with

streptokinase (6.3% vs. 7.3%)[10]. This translates into a 15% mortality reduction or about 10 lives saved per 1,000 patients treated.

RETEPLASE

Reteplase is a deletion mutant of t-PA that exhibits preferential activation of fibrin-bound plasmin and a two to threefold increase in half-life (15 min), permitting bolus administration. It has a lower affinity to fibrin (theoretically improving clot penetration), though similar fibrin specificity compared with alteplase. While initial studies showed superior infarct artery patency when compared with conventional dose t-PA in the RAPID I trial[62] and accelerated dose t-PA in the RAPID-2 trial[63], the GUSTO III study (15,059 patients) showed equivalent 30-day mortality rates with reteplase (7.5%) versus accelerated-dose alteplase (7.2%). The rates of the combined endpoint, death, or nonfatal MI-disabling stroke were similar: 7.98% and 7.91%, respectively[64].

Reteplase offers the advantage of double-bolus administration: 10 units IV followed by another 10 units 30 min later. Additionally, no weight adjustment is required.

TENECTEPLASE

Tenecteplase (TNK-t-PA) is the triple mutant form of t-PA that is highly fibrin-specific, exhibits decreased plasma clearance, and is resistant to plasminogen activator inhibitor (PAI-1) secreted by activated platelets. Its prolonged half-life

(~20 min) permits it to be dosed as a weight-adjusted 30–50 mg single bolus given over 2–5sec. The recommended dose is 30 mg for persons less than 60 kg, 35 mg for 60–70 kg, 40 mg for 70–80 kg, 45mg for 80–90 kg, and 50 mg > 90 kg.

Efficacy was demonstrated in the ASSENT II study (16,949 patients) that compared tenecteplase to accelerated dose t-PA. The incidence of death or nonfatal stroke was 7.11% for TNK-t-PA and 7.04% for t-PA. Intracranial hemorrhage occurred in 0.93% and 0.94%, respectively. There was a significantly lower incidence of major noncerebral bleeding, 4.66% and 5.94%, as well as all noncerebral bleeding, 26.4% vs. 29%, resulting in a lower need for blood transfusion in the TNK-t-PA group. The incidence of CABG (5.5% vs. 6.2%) and development of heart failure (6.1 vs. 7.0) were significantly lower in the TNK-t-PA group[65]. The 30-day mortality rates were virtually identical; this outcome met the predefined criteria for equivalence. As a single-bolus agent, tenecteplase has become the most widely used fibrin-specific agent.

Evidence exists that expeditious restoration of flow in the obstructed infarct artery after the onset of symptoms in STEMI patients is a key determinant of short- and long-term outcomes regardless of whether reperfusion is accomplished by fibrinolysis or PCI[37-39].

Efforts should be made to shorten the time for rapid recognition and treatment of patients with STEMI such that door-to-needle (or medical contact–to-needle) time for initiation of fibrinolytic therapy can be achieved within 30 minutes or that door-to-balloon (or medical contact–to-balloon) time for PCI can be kept under 90 minutes.

SELECTION OF REPERFUSION STRATEGY

Several issues should be considered in selecting the type of reperfusion therapy: Time From Onset of Symptoms: Time from onset of symptoms to fibrinolytic therapy is an important predictor of MI size and patient outcome[42]. The efficacy of fibrinolytic agents in lysing thrombus diminishes with the passage of time[43]. Fibrinolytic therapy administered within the first 2 hours (especially the first hour) can occasionally abort MI and dramatically reduce mortality[8,44].

Choice of reperfusion therapy is also affected by the patient's risk of bleeding. When both types of reperfusion are available, the higher the patient's risk of bleeding with fibrinolytic therapy, the more strongly the decision favours PCI. If PCI is unavailable, then the benefit of pharmacological reperfusion therapy is balanced against the risk.

STEMI patients presenting to a facility without the capability for expert, prompt intervention with primary PCI within 90 minutes of first medical contact undergo fibrinolysis unless contraindicated.

Primary percutaneous transluminal coronary angioplasty

If immediately available, primary PCI should be performed in patients with STEMI (including true posterior MI) or MI with new or presumably new LBBB who can undergo PCI of the infarct artery within 12 hours of symptom onset, if performed in a timely fashion (balloon inflation within 90 minutes of presentation).

Primary percutaneous transluminal coronary angioplasty (PTCA) is defined as balloon angioplasty undertaken as the primary reperfusion strategy for MI without previous or concomitant thrombolytic therapy[9]. Primary PTCA is better than thrombolytic therapy at reducing short-term major adverse cardiac events, including death in individuals with ST-segment elevation MI. These favourable results are sustained during long-term follow up too. Primary PTCA is associated with better clinical outcomes than thrombolytic therapy irrespective of the type of thrombolytic regimen used[9].

Specific considerations:

a. Primary PCI should be performed as quickly as possible, with a goal of a medical contact–to-balloon or door-to-balloon time of within 90 minutes.
b. If the symptom duration is within 3 hours and the expected door-to-balloon time minus the expected door-to-needle time is:
    i) within 1 hour, primary PCI is generally preferred.

ii) greater than 1 hour, fibrinolytic therapy (fibrin-specific agents) is generally preferred.

c. If symptom duration is greater than 3 hours, primary PCI is generally preferred and should be performed with a medical contact–to-balloon or door-to-balloon time as brief as possible, with a goal of within 90 minutes.

d. Primary PCI should be performed for patients younger than 75 years old with ST elevation or LBBB who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care

e. Primary PCI should be performed in patients with severe CHF and/or pulmonary edema (Killip class 3) and onset of symptoms within 12 hours. The medical contact–to-balloon or door-to-balloon time should be as short as possible (i.e., goal within 90 min).

Primary PCI is reasonable for selected patients 75 years or older with ST elevation or LBBB or who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock.

Patients with good prior functional status who are suitable for revascularization and agree to invasive care may be selected for such an invasive strategy.

It is reasonable to perform primary PCI for patients with onset of symptoms within the prior 12 to 24 hours and 1 or more of the following:

a. Severe CHF
b. Hemodynamic or electrical instability
c. Persistent ischemic symptoms[7]

If the expected door-to-balloon time exceeds the expected door-to-needle time by more than 60 minutes, fibrinolytic treatment should be considered unless it is contraindicated. This is particularly important when symptom duration is less than 3 hours but is less important with longer symptom duration, when less ischemic myocardium can be salvaged.

Assessment of the thrombolysis outcome

The assessment of successful thrombolysis is very important to plan for the next immediate step needed. This fact was recognised very early and many people have tried to assess the criteria by which a failed thrombolysis can be detected early. There have been many criteria that have been used for this purpose.

Relief of chest pain

Though relief of chest pain was recognised as one of the earliest markers of successful thrombolysis, it has many limitations. Although it predicts reperfusion with a sensitivity of 66-84% this happens in only 30-50% of patients and the specificity marker is below 30%[66-68]. Chest pain can be diminished or abolished

with opiates in many, including those with a persistently occluded vessel. Conversely, a persistent ache often occurs in those with an open vessel (possibly because of lack of tissue perfusion). As age, diabetes, pain threshold, and the development of pericarditis also influence pain, the presence or absence of pain is limited as a diagnostic test. The persistence or resolution of symptoms therefore does not have good predictive value in determining reperfusion status[67]. However, consideration of rescue techniques for those with continuing ischaemic pain may be one method of targeting those most likely to benefit. Since this clinical information is readily accessible and may be of value when used in conjunction with other markers[30], it is still used commonly to assess patients after thombolysis.

ECG criteria

Many ECG criteria have been examined. These include the ratio of the height of maximum ST elevation before and after treatment (usually measured 80 ms after the J point), the ratio of sums of ST segment elevation and/or depression, and the height of the T wave. The numerous studies investigating the relationship between ST segment resolution and patency of the infarct-related artery yield sensitivities of 52-97% with specificities of 43-88%[69-71].The criterion that appears to be most established is failure of the elevated ST segment (measured 80 ms after the J point in the lead of the 12 lead ECG with maximal ST elevation at baseline) to fall by 50% or more.

Equally importantly, a prompt reduction in ST segment shift appears to be associated with a better clinical outcome. In GISSI-2 (Gruppo Italiano per lo Studio della Sopravivenza nell'Infarcto Miocardico), patients with >80% reduction in ST elevation 4 hours after the initiation of therapy had less than half the in-hospital mortality rate of those with <20% reduction[72], while in ISAM (Intravenous Streptokinase in Acute Myocardial Infarction) early resolution of ST segment elevation was a powerful predictor of both early and late mortality after myocardial infarction[73]. There is consistent relation between degree of ST-segment resolution after thrombolysis and outcome. In the INJECT trials mortality was 17.5% in patients who achieved less than 30% ST segment resolution at three hours compared with 25% in those whose ST segments resolved by more than 70%[74-77].

Continuous ST monitoring using a varying number of ECG leads has been studied by several groups. This technique has revealed the very dynamic nature of the reperfusion process. ST segment monitoring is attractive in concept as this provides a means of assessing peak ST elevation, rather than its baseline level just before treatment starts. This could improve accuracy, but additional equipment is necessary and results must be available on-line for meaningful clinical use. ST segment and QRS vector analysis are other methods under evaluation but are not in routine clinical use.

Reperfusion arrhythmias are well recognised but are very insensitive for prediction of reperfusion. The early and frequent appearance of automatic idioventricular rhythm is perhaps the most useful marker of reperfusion and the absence of this rhythm can be incorporated as one of several criteria to help make the diagnosis of failed reperfusion.

Cardiac enzyme release

Measurement of cardiac enzyme release had become an integral part of the retrospective diagnosis of myocardial infarction, and the peak concentrations are useful in the process of risk stratification. In general, though, they have not proved very useful for immediate decision making in the management of acute myocardial infarction. A single measurement is not useful and even sequential measurements are difficult to interpret as the shape of the release curve relates to the time from onset of infarction (which is very variable) and to the thrombolytic agent used. There was considerable interest in biochemical tests for diagnosing failed thrombolysis. These included creatine kinase isoenzymes[78-80], troponin T[79] or I[80], fatty acid binding proteins and myoglobin[78-80]. Despite the high sensitivities and specificities described, none of these tests found favour in routine practice or were subjected to a prospective analysis in which the results influenced clinical decisions. Frequent blood sampling is often required and the determination of reperfusion sometimes depends on complex mathematical models.

Immunogenecity of Streptokinase

Streptokinase, a protein produced by beta haemolytic streptococci, is the most widely used and least expensive thrombolytic agent. However, a disadvantage to its use is its antigenicity due to the widespread presence of antibodies in the population, presumed secondary to previous streptococcal exposure or infection. The immunogenecity of STK was noted by Tillet and Garner[81] shortly after discovering its fibrinolytic effect. They found that STK was inactivated in blood samples from patients with recent Streptococcal infection as a result of the presence of neutralization of antibodies. A measurable level of antibodies to STK is nearly omnipresent in the population as a consequence of the high frequency of Streptococcal infection[11,16]. To induce a thrombolytic state, streptokinase must neutralise these antibodies as well as the endogenous inhibitors of fibrinolysis.

Studies in the general population in United Kingdom showed that 61% of the people had detectable IgG antibodies to streptokinase. However these titres varied from 0 to 490 with a median of 7 reflecting that antibody titres were generally low. Only a small percentage of subjects (10%) had high titres of streptokinase antibodies. No difference was found in the levels of antibody titre among different age groups or between sexes[82]. However this also showed that a proportion of the general population who had no previous streptokinase treatment could be as much at risk of an immune reaction to streptokinase as subjects who had received streptokinase earlier.

The prevalence of antistreptokinase antibodies in patients presenting to the coronary care unit for the first time is usually low and most are expected to respond to a standard dose of streptokinase. However most patients develop antibodies and streptokinase resistance by day 7 and upto 75% of patients treated once with streptokinase will be resistant to further treatment with streptokinase containing agents after two years[83]. The outcome from retreatment with streptokinase containing agents is likely to be unpredictable for a period beginning four to seven days after streptokinase dosage and lasting for more than two years. Other data suggest that this period may last for at least four years[84].

A similar high titre of antibody is expected in patients with recent streptococcal infection. Presence of such antibodies can have profound effects on the outcome of the thrombolytic therapy. Clinical failure of the activation of the fibrinolytic system by STK has been reported due to the presence of a high titre of ASTK antibodies[12]. In vitro clot lysis studies have demonstrated a significant reduction in the activation of plasminogen by STK between days 6 and 21 following STK therapy, a time when antibody titres are known to be high[85]. The presence of specific ASTK IgG antibodies has a major effect on the activity of STK in vitro. High circulating antibody titres to STK are likely to influence the efficacy of the thrombolytic state achieved, as well as causing the potential problems of adverse immune responses[86].

While it has been shown that the level of anti streptokinase antibodies is generally low in the population in western countries, the same does not hold true for patients from areas with high endemic streptococcal infections.

It has been shown that there is a significantly higher prevalence of ASTK antibodies in indigenous Australian patients with ACS compared with non indigenous long term residents (74% v 25%). These indigenous patients were concentrated in the, 54 age group, where ASTK antibody titres were highest, and mortality was seven to 12 times that of non-indigenous age matched controls[17]. Dramatically elevated anti streptokinase titre have been shown in the general aboriginal population in Australia who are subjected to endemic streptococcal infections[13].

It has been shown that the level of anti streptokinase antibodies in the Indian population also is higher. It may take twice the amount of streptokinase to neutralise these antibodies, than for the western population. This raises the doubt about the efficacy of the dose of SK being used now for thrombolysis in the Indian population[14].

Similarly, patients who have been exposed to STK earlier are likely to have ASTK antibodies that would be expected to neutralise the standard dose of STK.

To assess the outcome of presence of anti streptokinase antibodies on thrombolysis, many studies have been conducted. These studies have shown a varying picture of the response to thrombolysis.

An angiographic study showed that patients with persisting coronary occlusion at 24 hours tended to have higher anti-SK antibody titres[18]. However, another study from India[15] showed no relation between pretreatment ASTK antibody titres and reperfusion rates, although basal antibody values were relatively high in all patients, suggesting a potential compromise of the action of STK across the entire study population. A similar result was shown in another study from Pakistan where even though the antibody titre were high, they didn't seem to affect the outcomes of thrombolysis[16].

The effect of thrombolysis and its efficacy is hence to be proven beyond these doubts. With the introduction of primary PTCA as the treatment of choice for STEMI, it needs to be reassessed if the door to balloon time mentioned for the western countries holds true in the Indian population. With higher chances of failure of thrombolysis, late presentation of patients and the fact that the benefit of primary PTCA appears to be the same till a window period of 12 hours, a longer door to balloon period may be allowed in the Indian patients, especially when they are being planned for a fibrinolytic therapy with streptokinase and are likely to have high ASTK antibody titres.

MATERIAL AND METHODS

The study was conducted in the Department of Cardiology and Department of Microbiology at Christian Medical College (CMC) Vellore.

Patients presenting with acute STEMI to the casualty or the 'chest pain unit' were enrolled for the study, after an informed consent, if they satisfied the inclusion criteria.

Sample size

A minimum of 80 patients were to be recruited. 40 of these patients were to be those presenting within 6 hours of onset of chest pain and 40 with those presenting within 6-12 hours of onset of chest pain. However by the end of the study period, a total of 148 patients were included in the study.

Inclusion criteria

1. Patients with first episode of STEMI
2. Aged between 20-70 years
3. Presenting within 12 hours of onset of pain with no contraindications for thrombolysis
4. Not willing for a primary PTCA
5. No history of prior treatment with streptokinase

6. No other associated cardiac pathology like rheumatic heart disease, cardiomyopathies and congenital heart disease which could have had an effect on the one month survival and other clinical end points.

STEMI was diagnosed in any patient presenting with chest pain or discomfort and the electrocardiogram (ECG) showing ST segment elevation greater than 0.1 mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads. After ascertaining the absence of any contraindications these patients were thrombolysed with streptokinase. Those presenting beyond 12 hours duration are not recommended routinely for thrombolysis and hence were excluded.

Exclusion criteria

Since primary PTCA is the treatment of choice for the patients presenting with acute STEMI, they were offered this mode of therapy first and only those patients who were not willing for the same were enrolled for the study. Any other associated comorbities which could effect the clinical outcome if present was noted and such patient were excluded from the study. Also those patients who presented with cardiogenic shock or those who died within 30 minutes of initiation of thrombolytic therapy were also excluded as the outcome of these patients was unlikely to have been changed significantly by the thrombolytic therapy.

Sample collection and assessment of the response

In all the patients, 3-4 ml of blood was collected at the time of admission before the initiation of thrombolysis and was sent to the serology laboratory. The serum was further stored at -70^{o} C till the time of analysis for ASTK antibody titres.

All the patients were assessed for the criteria for reperfusion defined as:

- Resolution of chest pain in less than 90 min after start of thrombolysis
- Greater than 50% resolution of ST segment elevation in 2 contiguous leads showing maximum elevation in a 12 lead ECG taken 60 - 90 min after the thrombolytic therapy.
- Any reperfusion arrhythmia within 90 minutes of the thrombolysis. The arrythmias that were considered were accelerated idioventricular or junctional rhythm, transient second or third degree AV block not needing pacemaker support, acute sinus bradycardia (<50bpm), ventricular tachycardia or ventricular fibrillation.

Patients who had all 3 criteria were taken as responders and those with 2 were taken as probable responders and those with one or no criteria were taken as non responders.

Clinical end points – Major adverse cardiovascular events

The clinical end points were defined a below -

- Rest angina: The occurrence of any chest pain at rest, suggestive of angina, was taken as an episode of rest angina. This was irrespective of having taken any ECG during the episode or having taken any blood sample for estimation of cardiac enzymes.
- Heart Failure: Any episode of breathlessness needing hospitalisation and /or injectable diuretics for recovery was taken as an episode of heart failure unless diagnosed otherwise, provided the patient had documented left ventricular dysfunction as demonstrated by echocardiography at discharge or at the time of admission for breathlessness.
- Reinfarction: Any episode of acute chest pain with documented rise in the cardiac enzyme level by at least 2 times the normal level with or without new ECG changes was taken as an episode of re infarction.
- Death: Any patient dying without any demonstrable or diagnosed non cardiac cause during the period was taken as an episode of death due to cardiac cause.

All the patients recruited were counselled about the importance of regular medications and follow up. They were also contacted at 15-18 days of the event to enquire about the drug compliance and any clinical events. The patients were re-examined between 30-40 days of the clinical event and enquired about the clinical events at 30 days of the event. Those patients not reporting for review by

35 days were again contacted by phone or letter, for the review. All the data was collected by the principal investigator.

OBSERVATIONS AND RESULTS

Between 1st April 2009 and 28th February 2010 a total of 148 patients with acute ST-segment elevation myocardial infarction (STEMI) were enrolled into this study. The analysis of the data of these study subjects over a follow-up period of 30 days are shown below.

Statistical Methods

Data was entered using MS Excel and analyzed using STATA (STATACORP, TX, USA). Continuous variables were described using mean and standard deviation, if normally distributed. Variables which had skewed distribution were described using medians with range. The statistical significance of the association between the response and ASTK antibody levels was assessed using either chi-square test or fisher exact test (when expected cell count is <5). $P<0.05$ is considered as statistically significant.

Demographic data

Of the total patients almost 90% were males and the rest were females.

Table 1: Sex distribution

Sex	No. of patients	Percentage (%)
Male	133	89.86%
Female	15	10.14%
Total	148	100%

The mean and median age of the patients was 52 years. 11% of the total patients were under the age of 40 years.

Table 2: Mean and median age of the study subjects

	Mean±SD	Median	Min	Max
Age (years)	52±9.1	52	26	70

Table 3: Distribution of patients according to age

Age group	No. of patients	Percentage (%)
≤40 years	16	10.81%
>40 years	132	89.19%
Total	148	100%

The body mass index (BMI) was calculated for all the patients. The average BMI was around 25kg/m2. Nearly 42% of patients were overweight while almost 5% were obese.

Table 4: Body mass index range in patients

BMI (kg/m^2)	No. of patients	Percentage (%)
<20	8	5.41%
20-24.9	71	47.97%
25-29.9	62	41.89%
≥30	7	4.73%
Total	148	100%

Table 5: Distribution of body mass index (BMI) according to sex

	n	Mean±SD	min	max
Male	133	26.5±3.6	21	35
Female	15	24.9±2.9	18	34
Total	148	25.11±2.99	18	35

Risk factor analysis

Of the total patients almost 40% had diabetes mellitus and 37% had hypertension. More than 55% of patients were smokers. There were no smokers among the females. When taken this into account, 61% of the male patients were found to be smokers.

Table 6: Distribution of diabetes mellitus according to sex

Sex	Diabetes mellitus	
	Absent	Present
Male	82 (61.65%)	51 (38.35%)
Female	7 (46.67%)	8 (53.33%)
Total	89 (60.14%)	59 (39.86%)

Table 7: Distribution of hypertension according to sex

Sex	Hypertension	
	Absent	Present
Male	85 (63.91%	48 (36.09%)
Female	8 (46.67%)	7 (46.67%)
Total	93 (62.84%)	55 (37.16%)

Table 8: Distribution of smoking status according to sex

Sex	Smoking status	
	Non-smoker	**Smoker**
Male	51 (38.35%)	82 (61.65%)
Female	15 (100%)	0 (0%)
Total	66 (44.59%)	82 (55.41%)

The analysis of the serum lipid profile showed the following results. The average LDL level was 110.39 mg% with a median of 105.5 mg%. The average HDL was 33.73 mg% with a median of 33.5 mg%. The average TG was 159.14 mg% with a median of 129 mg%.

Table 9: Distribution of lipid profile according to sex

Sex	**TC** (mg/dl)	**TG** (mg/dl)	**HDL** (mg/dl)	**LDL** (mg/dl)
Male (n=130)	180.91±43.90	159.14±96.73	33.73±7.66	110.39±35.34
Female (n=15)	193.86±62.17	226.86±305.77	40.66±10.59	118.46±36.66
Total (n=145)	182.56±46.11	166.15±133.79	34.44±8.24	111.22±35.44

TC=Total cholesterol, TG=Triglyceride, LDL=Low density lipoprotein, HDL=High density lipoprotein

Time of presentation – Window Period

The average time to presentation after the onset of symptoms, termed the window period, was 345.54 min (5 hours, 45min) with a median of 300 min (5 hours). 46 patients presented directly to our centre with an average window period of 168.7 min (2 hours, 48 min). The average window period in the other patients was 425.29 min (7 hours, 5 min).

Table 10: Window period (in minutes) at presentation

Sex	n	Mean±SD	Median	Min	Max
Male	133	347.78±182.68	300	60	720
Female	15	325.66±193.73	270	30	660
Total	148	345.54±183.27	300	30	720

Table 11: Window period (in minutes) in patients presenting directly to us and those referred from elsewhere

	n	Mean	Min	Max
Presented directly	46	168.70	30	240
Referred	102	425.29	120	720
Total	148	345.54	30	720

Table 12: Number of patients with window period ≤6 and >6 hours

WP	No. of patients	Percentage (%)
≤360	94	63.51%
360+	54	36.49%
Total	148	100%

The distribution of STEMI involving different regions was as following:

Table 13: Myocardial infarction (MI) involving different territories

MI	No. of patients	Percentage (%)
Inferior wall MI	59	40.41%
Anterior wall MI	84	56.16%
Lateral wall MI	5	3.42%

Drugs prescribed and compliance at 30 days

The drugs prescribed at discharge were also noted. The prescriptions given for 5 important drugs was analysed which included aspirin, clopidogrel, a statin, a beta blocker and an ACE inhibitor/ ARB (angiotensin receptor blocker). The results were as following:

Table 14: Drugs prescribed at discharge

Drugs	No. of patients	Percentage (%)
All drugs – BB	2	1.36%
All drugs – ACE-I	2	1.36%
All drugs	142	96.60%
All drugs – BB – ACE-I	1	0.68%

BB=Beta-blockers, ACE-I=Angiotensin converting enzyme-inhibitors
All drugs include aspirin, clopidogrel, ACE-I/angiotensin receptor blocker, statins, beta-blockers

All the patients were also treated with an anticoagulant after thrombolysis. The same was prescribed for a minimum of 3 days. The three drugs used were Fondaparinux, Enoxaparin and Unfractionated heparin. The ratio of patients who received these different drugs was as following:

Table 15: Anticoagulant used

Anticoagulant	No. of patients	Percentage (%)
Fondaparinux	130	87.84%
Enoxaparin	10	6.76%
Unfractionated heparin	8	5.41%

The patients were followed up for 30 days and assessed for drug compliance. The following results were obtained. Almost 95% of the patients who did not have a MACE continued all the drugs prescribed to them. 2 patients were lost in follow up.

Table 16: Drugs at 30 days of follow-up in patients without MACE

Drugs	No. of patients	Percentage (%)
All drugs	110	95%
No drugs	6	5%
Total	116	

Antistreptokinase antibody titres

The antistreptokinase antibody titres were estimated in serial doubling dilutions starting from 40. So the titre values obtained were 0, 40, 80, 160, 320, 640, 1280, 2560, 5120 and 10240. The analysis showed the following results

Table 17: Mean and median anti-streptokinase antibody titres in the study subjects

	Mean±SD	Median	Min	Max
ASTK	717±1211	320	0	10240

Table 18: Distribution of levels of anti-streptokinase antibody titres

ASTK	No. of patients	Percentage (%)
0 - 40	30	20.27%
80 - 160	32	21.62%
320 - 640	47	31.76%
1280 and above	39	26.35%

Patients with one or no criteria for reperfusion were taken as non responders, those with 2 markers as probable responders and those with 3 markers as responders. The analysis showed that almost 37% of the patients had either one or no marker indicating that they were non responders and 63% of the patients were either responders or probable responders.

Table 19: Reperfusion markers of thrombolysis in the patients

Events	No. of patients	Percentage (%)
No reperfusion marker	18	12.16%
1 reperfusion marker	36	24.32%
2 reperfusion markers	33	22.30%
3 reperfusion markers	61	41.22%

Analysis of the response in relation to the window period showed the following.

Table 20: Comparison of different responses to thrombolysis in relation to the time of presentation

Response	Window period (min)		Total
	≤360	360+	
Non-responders	19 (35.18%)	35 (64.82%)	54 (36.49%)
Probable responders	24 (36.72%)	9 (27.28%)	33 (22.30%)
Responders	51 (83.61%)	10 (16.39%)	61 (41.2%)
Total	94 (63.51%)	54 (36.49%)	148 (100%)

We chose the median value of ASTK antibody titre as reference point to categorize into high titres and low titres. This was done because there was no established normal value for the general population and the values had a skewed pattern which affected the mean. The median value was 320.

The response to thrombolysis was analysed in relation to the presence of high (320+) titres or low (≤320) titres.

Table 21: Response of thrombolysis in patients with high ASTK antibody titres in relation to the time of presentation (Titre > 320+)

Response	Window period (min)		Total
	≤360	360+	
Non-responders	19 (50.0%)	19 (50.0%)	38
Probable responders	7 (87.5%)	1 (12.5%)	8
Responders	13 (92.86%)	1 (7.14%)	14
Total	39 (65.0%)	21 (35.0%)	60

p=0.006 (Fisher's exact test)

Table 22: Response of thrombolysis in patients with low ASTK antibody titres in relation to the time of presentation (Titre ≤320)

Response	Window period (min)		Total
	≤360	360+	
Non-responders	0 (0%)	16 (100%)	16
Probable responders	17 (68%)	8 (32%)	25
Responders	38 (80.85%)	9 (19.15%)	47
Total	55 (62.5%)	33 (37.5%)	88

p<0.001

In patients who presented with window period of <6 hours, 69% of responders had titres ≤320 while 100% of non-responders had a titre of >320.

Table 23: Response to thrombolysis in patients presenting with window period ≤360 min (≤6 hours)

ASTK	Response to thrombolysis			Total
	Non-responders	Probable responders	Responders	
≤320	0 (0%)	17 (30.91%)	38 (69.09%)	55 (100%)
320+	19 (48.72%)	7 (17.95%)	13 (33.33%)	39 (100%)
Total	19 (20.21%)	24 (25.53%)	51 (54.26%)	94 (100%)

p<0.001

In patients who presented with window period >6 hours, only 48% of patients with titres ≤320 were non-responders while 90% of patients with titre >320 were non-responders.

Table 24: Response to thrombolysis in patients presenting with window period >360 min (>6 hours)

ASTK	Response to thrombolysis			Total
	Non-responders	Probable responders	Responders	
≤320	16 (48.48%)	8 (24.24%)	9 (27.27%)	33 (100%)
320+	19 (90.48%)	1 (4.76%)	1 (4.76%)	21 (100%)
Total	35 (64.81%)	9 (16.67%)	10 (18.52%)	54 (100%)

p=0.007

Further, the 'responders' and 'probable responders' were grouped as patients having benefited from thrombolysis and the 'non responders' as not having benefited from thrombolysis.

Further analysis in these two categories showed that, within a window period of 6 hours, the patients who benefited from thrombolysis were more likely to have lower ASTK antibody titres while all the patients who did not benefit had high ASTK antibody titres.

Table 25: Benefit of thrombolysis in patients with window period less than 6 hours (≤360 min)

ASTK	Benefit of thrombolysis		Total
	No	Yes	
≤320	0 (0%)	55 (73.33%)	55 (58.51%)
320+	19 (100%)	20 (26.67%)	39 (41.49%)
Total	19 (100%)	75 (100%)	94 (100%)

p<0.001

Similarly patients who presented after 6 hours and had benefited from thrombolysis were more likely to have lower ASTK antibody titres while more than 50% of those who did not benefit, had high titres.

Table 26: Benefit of thrombolysis in patients with window period more than 6 hours (360+ min)

ASTK	Benefit of thrombolysis		Total
	No	Yes	
≤320	16 (45.71%)	17 (89.47%)	33 (61.11%)
320+	19 (54.29%)	2 (10.53%)	21 (38.89%)
Total	35 (100%)	19 (100%)	54 (100%)

p=0.002

The benefit of thrombolysis in relation to the varying antibody titres also showed a significant relation, with patients having titre more than 1280, more likely not to have benefited from thrombolysis than those with lower titres.

Table 27: Benefit of thrombolysis in relation to the varying antibody titres

ASTK	Benefit of thrombolysis		Total
	No	Yes	
0 - 40	8 (26.67%)	22 (73.33%)	30 (100%)
80 -160	5 (15.63%)	27 (84.38%)	32 (100%)
320 - 640	12 (25.53%)	35 (74.47%)	47 (100%)
1280 and above	29 (74.36%)	10 (25.64%)	39 (100%)
Total	54 (36.49%)	94 (63.51%)	148 (100%)

p<0.001

Risk factors in patients less than 40 years old

The risk factor analysis was done in a small subgroup of patients who were aged less than or equal to 40 years. Though the numbers were small to show any statistically significant result, 75% of the patients in this subgroup were smokers. The average window period was however shorter in this subgroup compared to the total average.

Table 28: Lipid profile and window period in age <40 years (n=16)

Lipids	Mean±SD	Median	Min	Max
LDL (mg/dl)	102.43±22.89	101.5	66	139
HDL(mg/dl)	35.25±10.46	35.0	21	62
TG (mg/dl)	172.06±63.79	167.5	94	309
WP (min)	297.18±186.67	272.5	60	660

LDL=Low density lipoprotein, HDL=High density lipoprotein, TG=Triglycerides, WP=Window period (min)

Table 29: Distribution of common risk factors in patients with age <40 years

	No. of patients	Percentage (%)
Diabetes mellitus	1	6.25%
Hypertension	2	12.50%
Smoker	12	75.00%

Analysis of the major adverse cardiovascular events

Patients were followed up for 30 days for any major adverse cardiovascular events (MACE). The MACE that were looked for were death, reinfarction, rest angina and congestive cardiac failure. 2 patients were lost during follow up.

Table 30: Incidence of major adverse cardiovascular events (MACE)

MACE	No. of patients	Percentage (%)
Absent	116	79.45%
Present	30	20.55%

The different events which were noted are shown in the table. As seen rest angina was the most common MACE of all the four.

Table 31: Different events recorded as MACE at 30 days

MACE	No. of patients	Percentage (%)
Death	5	16.67%
Reinfarction	4	13.33%
Rest angina	15	50.00%
Congestive cardiac failure	6	20.00
Total	30	100%

The relation of presence of MACE in relation to the time of presentation showed that MACE was more likely in those who presented after a window period of 6

hours. The numbers were however not enough to give any statistical significance.

Table 32: MACE in patients depending on the time of presentation

MACE	Window period (min)		Total
	≤360	360+	
Absent	77 (66.38%)	39 (33.62%)	116 (100%)
Present	16 (53.33%)	14 (45.67%)	30 (100%)
Total	93 (63.70%)	53 (36.30%)	146 (100%)

p=0.185

The occurrence of MACE was further analysed in relation to the presence of low or high ASTK antibody titres. This showed that patients without MACE were more likely to have low titres and those with MACE were more likely to have high titres. This relation was statistically significant.

Table 33: MACE in patients depending on the antistreptokinase antibody titres

MACE	ASTK		Total
	≤320	320+	
Absent	74 (63.79%)	42 (36.21%)	116 (100%)
Present	13 (43.33%)	17 (56.67%)	30 (100%)
Total	87 (59.59%)	59 (40.41%)	146 (100%)

p=0.042

Further the MACE was analysed separately in patients with high and low titres who had presented before 6 hours and those who presented after 6 hours. In both the groups the patients with higher titres were more likely to have MACE than those with lower titres.

Table 34: MACE in patients with high and low titres with window period <6 hours (360 min)

MACE	Window period (min)		Total
	≤320	320+	
Absent	48 (62.34%)	29 (37.66%)	77 (100%)
Present	6 (37.50%)	10 (62.50%)	16 (100%)
Total	54 (58.06%)	39 (41.94%)	93 (100%)

p=0.067

Table 35: MACE in patients with high and low titres with window period >6 hours (360 min)

MACE	Window period (min)		Total
	≤320	320+	
Absent	26 (66.67%)	13 (33.33%)	39 (100%)
Present	7 (50.00%)	7 (50.00%)	14 (100%)
Total	33 (62.26%)	20 (37.74%)	53 (100%)

p=0.270

DISCUSSION

Ischemic heart disease is the leading cause of death in both the developing and the developed countries[1]. The fact that it is estimated to rise further and faster in the developing countries is a matter of concern. India is going to have a significant proportion of the total number of such cases in the world in the near future. As discussed earlier, it has also been shown that in India a larger proportion of those with acute coronary syndromes (ACS) present with ST elevation myocardial infarction (STEMI) than those in the developed countries[6]. However the vast majority of the population doesn't have access to the optimal hospital care for this acute emergency. While the optimum management needs an immediate reperfusion by primary PTCA, there are very limited centres which can offer this treatment. The significant majority of the population is treated with thrombolytic therapy[6].

There are many thrombolytic agents which have been approved for use. The fibrin specific agents have a better mortality benefit than STK, saving upto 10 lives per 1000 patients treated[10]. However, the fibrin selective agents are many times the cost of STK making STK the most commonly used thrombolytic agent in most developing countries. However a fact to be noted is that almost all the studies that have been done to assess the efficacy of these agents were conducted in the western population. It has been proven that the action of streptokinase is neutralised in the presence of anti streptokinase

antibodies[12,13,83,86,87], which are formed in the body in response to the streptococcal infections. These infections are very common in the developing countries like India and it has been proven in earlier studies that the anti streptokinase antibody titres are much higher in the subcontinental population than in the developed countries[14,16,82]. Under these circumstances doubts have been raised about the efficacy of streptokinase to treat STEMI[12,13,17,19]. Studies have been conducted earlier to address this concern but they did not give a definite evidence and there were too few studies to draw any firm conclusion. Also these studies did not take into account the window period at presentation which could have also significantly affected the outcome of thrombolysis by streptokinase. It is now a well proven fact that the efficacy of thrombolysis decreases proportionately with the time duration from onset of symptoms with the maximum benefit in the first 2 hours[7,42-45].

This study was conducted with a primary objective of assessing the effect of ASTK antibodies on the response to thrombolysis and occurrence of MACE while taking into account the window period at presentation. The patients were analysed in two separate groups with window period less than 360 minutes (6 hours) and more than 360 minutes.

While planning the study it was thought to enroll a minimum of 80 patients with forty each in two groups with window period <360 minutes (6 hours) & >360minutes and again at least 20 each in two groups of high & low ASTK

antibody titres. During the course of the study a total of 148 patients were enrolled after taking an informed consent.

Demographic results

Nearly 90% of the patients were males (Table 1). This was similar to the pattern seen in the CREATE registry[6] in which more than 80% of patients with STEMI were males. The increased number could be attributed to two possible factors: the proportion of males in patients with STEMI is higher, and also it was noted that female patients were more hesitant in giving consent to be part of a study.

Analysis of the different age groups showed that average and median age was 52 years. There were 16 patients below the age 40 which formed almost 11% of the total (Table 2&3).

The body mass index (BMI) analyzed showed that almost 42% of patients were overweight and 5% were obese (Table 4).

The risk factors analysis showed that almost 40% of the patients had diabetes mellitus and 37% had hypertension (Table 6-9). While the total percentage of patients who were smokers was 55%, none of them were females. This showed that almost 62% of the male patients were smokers. This proportion is quite high from the proportion of patients who were smokers in the CREATE registry. However Begom & Singh in 1995 had reported a higher prevalence of smoking in

south Indian males which was close to 45%[87]. Considering that the prevalence of smoking has increased over the past decade, this could be taken as the present prevalence of smoking among males, especially in the lower socioeconomic strata. The prevalence of diabetes mellitus and hypertension was similar to what was seen in the previous registry.

The analysis of the lipid profile showed that the mean LDL was 111mg%, HDL was 34mg% and triglyceride was 166mg%. All of these values represent suboptimal values which can predispose to CAD.

The data was analysed separately in patients with age <40 years to assess the risk factors in this subset of young patients (Table 28 & 29). While there was not much difference in the prevalence of diabetes mellitus, hypertension or dyslipidemia, there was a strikingly high prevalence of smoking in this group. 75% of the patients in this group were smokers and if the 2 female patients are excluded from this, 86% of the male patients were smokers. This shows the importance of smoking as an important risk factor for ischemic heart disease, especially in the young.

Window period

Another very important factor affecting the prognosis in patients presenting with STEMI is the time of presentation after the onset of chest pain, known as the window period[7,42-45]. The mean window period in our study group was 345min (5

hours, 45 min) with a median of 300 min (5 hours) which is longer than what is seen in the developed countries[4]. 21 patients had presented within a window period of 3 hours which was only 14% of the total. Almost 64% of the patients presented within 6 hours of onset of pain. Only 46 patients had presented directly to our centre and the rest of the 102 patients were referred from some other hospital (Table 10,11,12). In patients who presented directly to us, the mean window period was 168 min (2 hours, 48 min) with a range of 30-240 min. While the mean window period of the patients who were referred from elsewhere was 425 min (7 hours, 5 min) with a range of 120-720 min. The history taken from these patients suggested that most of the delay was due to time taken up for referral from the peripheral hospital and the travel time. The first medical contact of most of the patients was much shorter than the actual window period of thrombolysis. This is a striking observation as the mean window period differed by more than 4 hours. This shows that a lot of mortality and morbidity can be decreased if the importance of early thrombolysis and prompt referral is reinforced in the primary physicians who are often the first medical contact of the majority of the patients.

Of the total patients, 56% had anterior wall STEMI, while 40% had inferior wall MI, with varying combination of right ventricular MI and posterior wall involvement, and only 4% were diagnosed to have an isolated lateral wall MI.

Compliance with drugs at 30 days

All the patients were counselled regarding regular medical therapy. The prescription pattern of 5 important drugs was also analysed which included aspirin, clopidogrel, a statin, betablocker and an ACE inhibitor/angiotensin receptor blocker (Table 14-16). 97% of the patients were prescribed all the 5 essential drugs. Of the patients who did not have any major adverse cardiovascular events (MACE), 95% of the patients continued to take the treatment as advised, 5% had stopped the prescribed medications and 2 patients were lost to follow up. This showed the possible beneficial effect of spending a few minutes extra on counselling the patients about the importance of drug compliance. The high compliance could have also been due to the close follow up of these patients acting as intermittent reminders for drug compliance.

All the patients were also given anticoagulant therapy for at least 3 days post thrombolysis. The majority of the patients received Fondaparinux for this purpose.

Anti streptokinase antibody titres

The ASTK antibody levels were assessed by particle agglutination method using a commercial kit, SERODIA – ASK, supplied by FUJIREBIO, Tokyo, Japan. The method used in earlier studies to assess the ASTK antibody levels included the clot lysis assay which is a highly sensitive method to measure the streptokinase-neutralising capacity in serum and an enzyme-linked

immunoassay (EIA) to measure streptokinase-binding IgG. The particle agglutination method has been assessed in comparison to the earlier methods and has correlated well with serum neutralising capacity[88].

The mean anti-streptokinase antibody levels were 717±1211, however, the range varied from minimum of 0 to a maximum of 10240 (Table 17). Since the extreme values were affecting the average ASTK antibody titre, it was decided to take the median value of 320 units as the reference point. Patients with titres ≤320 were taken as having low titres and those with >320 were taken as high titres.

Patients were assessed for the clinical evidence of reperfusion which were defined as

- Resolution of chest pain in less than 90 min after start of thrombolysis
- Greater than 50% resolution of ST segment elevation in 2 contiguous leads showing maximum elevation in a 12 lead ECG taken 60-90 min after the thrombolytic therapy.
- Any reperfusion arrhythmia within 90 minutes of the thrombolysis

Patients who had all 3 criteria were taken as responders and those with 2 criteria were taken as probable responders and those with one or no criteria were taken as non responders.

Of the total patients, 61 (41.21%) were responders, 33 (22.3%) were probable responders and 54 (36.49%) were non responders (Table 20). These results

confirm to those reported earlier from the Indian subcontinent by Shaila et al[15] (48% responders, 28% probable responders and 28% non responders) and Kazmi et al[16] (42% responders, 37% probable responders and 21% non responders). The percentage of non responders in our study appeared to have been more than those in these two studies. This could have been due to the fact that the ASTK antibody titres are higher in the south Indian population as shown earlier by Alexander et al[14].

Effect of time

The effect of time was also analysed in patients with high and low ASTK antibody titres (Tables 21 &22). More than 90% of the responders with high titres had presented before 6 hours. Similarly in patients with low titres, more than 80% of the responders presented before 6 hours while all the non responders presented after 6 hours. This showed that patients were more likely to respond to thrombolysis when they present early to the hospital independent of the presence of low ($P<0.001$) or high ($P=0.006$) ASTK antibody titres. This reinforces the already known fact that time is a very important factor in the management of STEMI and the patient needs to receive a reperfusion therapy at the earliest.

Effect of titre

The response to thrombolysis was analyzed in subjects presenting before and after 6 hours window period and the effect of titre on the response was assessed (Tables 23 & 24). In patients with a window period of <6 hours 75% of

responders had titres ≤320. Further, of all patients with titres ≤320, 69% of patients were responders, which was significantly higher than in patients with titres >320 in which only 33% of patients were responders. Of the non-responders, all the patients (100%) had titres of >320 ($p<0.001$). In the group of patients with a window period >6 hours, among patients who had a titre of >320, 90% were non-responders, while among those with titres <320, 48% patients were non-responders ($p=0.007$). This shows that irrespective of the window period, ASTK antibody titres impaired thrombolysis. The effect was particularly pronounced and highly significant in patients who presented with a window period of <6 hours and had high titres. This represents a group at significant loss who, inspite of presenting early to the hospital have an inadequate response to treatment with streptokinase because of high ASTK antibody titres.

Patients were divided into 2 groups for further analysis. ‘Non responders’ were grouped as having not benefited from thrombolysis and ‘responders’ and ‘probable responders’ were grouped as having benefited from thrombolysis. The effect of the ASTK antibody titres was analysed in two separate groups with window period less than 6 hours and window period more than 6 hours (Tables 25, 26 & 27).

In the patients with window period <6 hours, 73% of those who benefited from thrombolysis had titres less than or equal to 320 while only 27% had titres more than 320. All the patients who did not benefit from thrombolysis had high titres of

>320 (P <0.001). In patients who had a window period of > 6 hours, 89% of those who benefited from thrombolysis had low ASTK antibody titres and almost 54% of those who did not respond had high titres (P=0.002).

When the benefit of thrombolysis was assessed in different groups with varying titres of ASTK antibodies, it was seen that more than 75% of the patients in each group of ASTK antibody titre upto 640 had benefited from thrombolysis while almost 75% of patients with titres of 1280 or above had not benefited from thrombolysis (P<0.001) (Table 27).

These results are similar to those observed earlier by Juhlin et al. They also showed that an elevated anti streptokinase titre was present in patients without signs of reperfusion. The failure of reperfusion could be due to the neutralization of streptokinase by the antibodies in the serum. This has also been shown by Urdahl et al[13] in the rural aboriginal community in Northern Australia where the high anti streptokinase titres in some cases were sufficient enough to neutralize the conventional dose of 1.5 million units streptokinase. The population studied in their study had high incidence of endemic streptococcal infection resulting in the high antibody titres.

Buchalter et al[83] have also shown that patients who are treated with streptokinase once, develop higher titres of anti STK antibodies leading to resistance to subsequent retreatment with streptokinase upto 24 months. Patel et

al[89] have shown presence of anti streptokinase antibodies in the serum upto 866 days after having been treated with streptokinase for STEMI. Lynch et al[87] similarly showed that treatment with streptokinase is unlikely to induce an effective thrombolytic state in patients with high ASTK antibody titres. Numerous other studies also support these observations[12,17,18,86]. The ACC/AHA guidelines mention the exposure to streptokinase, 5 days before the day of presentation, as a relative contraindication for thrombolysis with STK[7].

Our study results however vary from the earlier studies by Shaila et al[15] and Kazmi et al[16] who showed no effect of anti streptokinase antibodies on reperfusion. However in the study by Shaila et al the total number of patients who underwent thrombolysis was 25. This could have been a small number to assess the actual effect of ASTK antibody titres on benefit of thrombolysis. In the study by Kazmi et al, the window period of the patients undergoing thrombolysis was not taken into factor. As has been proven earlier and also evident from our study, the window period has a significant effect on the outcome of thrombolysis in patients with both high and low titres. Our study showed that the response to thrombolysis is impaired in patients with high ASTK antibody titres in patients with shorter as well as longer window period. The rates of reperfusion and benefit from thrombolysis was significantly higher in patients with low titre than in high titre.

Our study shows that presence of ASTK antibodies significantly affects the outcome of thrombolysis in patients with acute STEMI presenting both before or after a window period of 6 hours. A significant proportion of the population in developing countries like India is likely to have a high titre of anti streptokinase antibody titres, in view of the high incidence of streptococcal infection in the population. The efficacy of streptokinase in patients with STEMI and high ASTK antibody titres may be doubtful thus affecting the outcome in a significant proportion of the patients.

In view of these findings there needs to be a rethink in using streptokinase as the first line of thrombolytic agent. It may be preferable to use fibrin specific agents like alteplase, tenecteplase or reteplase. These agents have shown better outcomes than STK, as discussed earlier, in the western population which is likely to have low ASTK antibody titres. The benefit of these agents in a population with high ASTK antibodies will be expected to be much more than reported earlier.

Though it needs a larger comparative study, our study prompts us to think that instead of thrombolysis with STK, in patients with high ASTK antibody titres, it may be worthwhile to shift the patient for primary PTCA when there is not an undue delay in the process and a fibrin selective agent is not available. The current recommendation of a maximum allowable time difference of 60 minutes between door to needle & door to balloon time may be relaxed. Though we are in

no position to recommend a particular duration that can be allowed, it may be worth conducting a trial to compare the results between thrombolysing with streptokinase and doing a primary PTCA with a longer door to balloon time allowed in patients with high ASTK antibody titres. However if the primary centre can thrombolyse with a fibrin specific agent, it should be preferred to a delayed primary PTCA.

Finally if a kit for rapid analysis of the level of anti streptokinase titres can be developed, it may help us in deciding the thrombolytic agent to be used. This kit may also be useful in stratifying patients so that those with low titres may be thrombolysed with streptokinase while those with high titres may be planned for a primary PTCA.

Major adverse cardiovascular events

Another important part of our study was to follow up the patients and assess the occurrence of major adverse cardiovascular events (MACE) at 30 days of STEMI (Table 30 &31). The MACE that were looked for included either death, reinfarction, rest angina or congestive cardiac failure (CCF). Of the total 148 patients, 146 patients were followed for 30 days and 2 were lost in follow up. 30 patients had a MACE which formed 21% of the total individuals. 50% of the total MACE was because of rest angina, almost 20% due to CCF, 17% due to death and 13% because of reinfarction. The number of deaths in the entire cohort was 5 which amounted to a 30 day mortality rate of 3.5%. This was much less than

what has been observed in other registries. This could be due to the fact that this study was not designed to assess the mortality in patients with STEMI and many patients were excluded from the study because of the strict inclusion criteria. As a result a relatively low risk subset of patients only must have been part of this study.

Analysis of MACE in relation to window period (Table 32) showed that among the patients who had a MACE, 47% had presented after 6 hours while in those without a MACE only 34% had presented after 6 hours (P=0.18). This showed that more number of patients with MACE had presented with a longer window period. More numbers may be needed to show the statistical significance of this observation.

When a relation was sought between anti streptokinase titres and MACE, it was seen that almost 57% of patients with MACE had titres of >320 while only 36% of patients without MACE had similar titres (P=0.042). It was hence evident that the patients with higher ASTK antibody titres were more likely to have a MACE (Table 33). This could be an indication of the higher chances of failure of thrombolysis in this group. It also shows that ASTK antibody titres can act as a prognostic marker for the adverse outcomes in patients of STEMI who are thrombolysed with streptokinase. These patients may then warrant more attention than the others.

To account for the effect of the window period on the MACE, the MACE was analysed in two separate groups with window period <6 hours and >6 hours and the effect of high and low antibody titres was assessed (Table 34&35). In patients with window period less than 6 hours, almost 63% of those with MACE had titres of >320 while only 38% of those without MACE had a similar titre (P=0.067). In patients with window period more than 6 hours 50% of those with MACE had titres > 320 while 33% of those without MACE had similar titres (P=0.27). In both the subgroups the relationship of higher MACE with higher ASTK antibody titres appeared to have been preserved though the numbers in individual groups were not enough to give a statistical significance.

Our results showed a significantly higher incidence of MACE in patients with high anti streptokinase titres. The other studies conducted previously had not assessed the clinical outcome and this was a very important outcome seen in our study. The effect seemed to be especially more evident in the group with window period of less than 6 hours. This group is expected to have a better response in view of the shorter time to thrombolysis but the results show that presence of anti- streptokinase antibodies may impair the advantage of a shorter window period. An indication of higher antibody titres in those with MACE remained in those with window period of >6 hours too, though it was not statistically significant. However, the results seem to imply that the presence of high anti streptokinase titres act as a poor prognostic factor for any given patient with a higher chance of developing MACE in the following 30 days.

SUMMARY AND CONCLUSIONS

- The mean window period at presentation in patients with STEMI is longer in India.
- Patients presenting directly to the treating hospital had mean window period of 2 hours 48 minutes
- Significant amount of time was lost in patients who were referred for treatment with the mean window period being 4 hours more than patients presenting directly.
- Smoking is a very important risk factor in the male patients, especially those below the age of 40 years.
- Anti streptokinase antibodies are widely prevalent in the general population
- These antibodies when present in high titres impair the reperfusion effect of streptokinase
- Patients who responded to thrombolysis were more likely to have low anti streptokinase titres while the non-responders had higher titres.
- The benefit of thrombolysis was significantly better in patients with low anti streptokinase titres compared to those with high titres.
- This pattern was seen in both patients presenting before and after a window period of 6 hours.

- The effect of high titres was particularly evident in patients who presented before 6 hours. In these patients the advantage of early presentation is partially lost by the high anti streptokinase titres.
- There was a significant effect of time on reperfusion by thrombolysis. Those presenting early were more likely to respond to thrombolysis than those presenting late.
- There was a direct correlation between high anti streptokinase titres and occurrence of major adverse cardiovascular events (MACE).
- Patients with MACE were more likely to have high anti streptokinase titres than those without MACE. This trend was evident in both patients presenting before and after 6 hours window period.
- The anti streptokinase titres can hence be used as a prognostic marker in patients presenting with STEMI & treated with streptokinase.
- High ASTK antibody titres blunt the response to thrombolysis and act as a poor prognostic marker in patients with STEMI who are treated with STK. Fibrin specific thrombolytic agents like alteplase, reteplase and tenecteplase may be preferable for thrombolysis, especially in those who are from areas with high endemic streptococcal infections.

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Abbreviations

ACS	-	Acute coronary syndrome
ASTK	-	Anti streptokinase
CAD	-	Coronary artery disease
CVD	-	Cardiovascular disease
STEMI	-	ST segment elevation myocardial infarction
PTCA	-	Percutaneous transluminal coronary angioplasty
STK	-	Streptokinase
ECG	-	Electrocardiogram
WHO	-	World Health Organisation
IHD	-	Ischemic heart disease
MI	-	Myocardial Infarction
LV	-	Left ventricle
PCI	-	Percutaneous coronary intervention
t- PA	-	Tissue type plasminogen activator
LBBB	-	Left bundle branch block

Abbreviations used in the master chart

Hosp N	-	Hospital number
Name	-	Name of the patient
Sex	-	Patient gender (0- male , 1- female)
Age	-	Age of the patient in years
Weight	-	Weight in kilograms
Height	-	Height in meters
RES	-	Resolution of the ST segment by >50% (0 – No resolution, 1 - resolution present)
REL	-	Relief from chest pain within 90 minute of thrombolysis (0– No relief, 1- Relief present)
ARRY	-	Reperfusion arrhythmias (0- absent, 1- present)
RESP	-	Response to thrombolysis (0,1 – non responders, 2 – probable responders, 3 – responders)
WP	-	Window period (in minutes)
DM	-	Diabetes mellitus (0- absent, 1- present)
HTN	-	Hypertension (0- absent, 1- present)
Smoker	-	Smoking status (0- non smoker, 1- smoker)
TC	-	Total cholesterol (in mg/dl)
TG	-	Triglycerides (in mg/dl)
HDL	-	High density lipoproteins (in mg/dl)
LDL	-	Low density lipoproteins (in mg/dl)

MI - Area involved in myocardial infarction (0 – Inferior wall STEMI, 1- anterior wall STEMI, 2- lateral wall STEMI)

Drug - Drugs prescribed at discharge (5 - All 5 essential drugs , 0 – beta blocker not given, 1 – ACE inhibitor/ ARB not given, 15 – both beta blocker and ACEI/ARB not given)

F/C - Anticoagulant used (0- Fondaparinux, 1- Enoxaparin, 2- Unfractionated heparin)

30 d - Drug compliance at 30 days (All 5 essential drugs – 5, 0 – beta blocker not given, 1 – ACE inhibitor/ARB not given, 15 – both beta blocker and ACEI/ARB not given)

MACE - Major adverse cardiovascular event

Event - MACE that occurred (0 – death, 1- reinfarction, 2- rest angina, 3- congestive cardiac failure)

ASTK - Anti streptokinase antibody titres

CMC - first medical contact (1- presented directly to our centre, 0- referred from elsewhere)

STUDY Proforma

Patient Hospital No:_____

Drug: _____

Name : Sex: M ☐ F ☐

Age :

Address :

Phone No:

Height: Weight:

Date of STEMI :

Window period : _____ hours.

If > 3 hours, reason for delay : Ignored pain
- Went to local hospital and referred
- Travel > 90mins
- Any other

☐ Diabetes Mellitus ☐ Hypertension ☐ Smoking

Socio-Economic Status:

- Monthly Income

☐ < Rs.2,000/-

☐ Rs.2,000/- to Rs.5,000/-

☐ Rs.5,000/- to Rs.10,000/-

☐ >Rs.10,000/-

Educational Status:

Self	☐ Un educated / Matriculation	Immediate Attender	☐ Un educated / Matriculation
	☐ Undergraduate		☐ Undergraduate
	☐ Post - graduate		☐ Post - graduate

ECG diagnosis -

ST elevation in -

Response to thrombolysis:

1. Resolution of ST segment elevation by >50% in 2 contiguous leads ☐Yes No☐
2. Relief from pain within 90min of thrombolysis ☐ Yes ☐ No
3. Reperfusion arrhythmia ☐ Yes ☐ No

☐ VT ☐ VF ☐ AV Block ☐ S. Bradycardia

☐ Others

Adverse Event:

☐ Hypotension ☐ Bleeding ☐ Anaphylaxis

☐ Any other _____

Echo Cardiographic Findings

Echo Cardiographic	***At Discharge***	***After 1 month***
LVEF		
E		
A		
E/A		
DECT		
MR		

Review at 15th day

- Any hospital admission ☐ Yes ☐ No
- Rest angina ☐ Yes ☐ No
- Heart failure ☐ Yes ☐ No
- Reinfarction ☐ Yes ☐ No
- Death ☐ Yes ☐ No

Drugs

Drugs	***At Discharge***	***After 1 month***
Aspirin		
Clopidogrel		
Statins		
ACE Inhibiters		
ARBs		
B – Blockers		
Fondaparinux		
Enoxaparin		
Others		

Review after 30 days.

- Any hospital admission ☐ Yes ☐ No
- Rest angina ☐ Yes ☐ No
- Heart failure ☐ Yes ☐ No
- Reinfarction ☐ Yes ☐ No
- Death ☐ Yes ☐ No

Dr. Subhendu.

Hosp No	Name	Sex	Age	WEIGHT	HEIGHT	RES	REL	ARRY	RESP	WP	DM	HTN	SMOKER	TC	TG	HDL	LDL	MI	Drug	F/C	30 d	MACE	Event	ASTK	CMC
415175d	Velayutham	0	61	69	1.8	1	1	0	2	240	1	1	1	108	87	22	65	1	5	2	5	0		0	1
129225b	Niyaz S k	0	42	80	1.74	1	1	0	2	225	0	0	1	143	67	29	94	0	5	1	5	0		80	1
082405b	Kuppuswamy	0	66	73	1.64	1	1	1	3	90	1	1	1	197	78	30	149	2	5	1	5	0		0	1
423817d	Damodaram	0	64	70	1.59	1	1	0	2	390	1	1	1	100	70	23	59		5	0	5	0		160	0
478548d	Sampath Raj	0	56	70	1.56	1	1	1	3	300	0	0	1	144	233	23	77	0	5	0	5	0		320	0
480495d	Ravichandran	0	48	66	1.56	1	1	1	3	60	0	0	0	192	98	39	106	1	5	0	5	0		160	1
432035d	Selvam R	0	65	52	1.65	1	1	1	3	60	0	0	1	159	85	33	102	0	5	0	5	0		160	1
432124d	Selvam C	0	37	65	1.65	1	0	0	1	240	0	1	1	122	105	21	78	0	5	0	5	1	2	1280	0
417772d	Manohari	1	55	57	1.52	0	1	0	1	660	1	1	0	228	135	39	166	0	5	2	5	0		320	0
418899d	Kannammal	1	54	57	1.55	1	1	0	2	170	0	1	0	168	119	35	105	1	5	0	5	1	3	640	1
432217d	Lakshmi	1	65	65	1.61	0	0	1	1	420	0	1	0	257	165	39	194	1	5	0	5	1	1	40	0
480316d	Veeraswamy	0	56	68	1.64	1	1	1	3	120	0	0	1	205	95	34	134	0	5	0	5	0		320	1
480312d	Ravi Shankar	0	50	72	1.74	1	1	1	3	360	0	0	1	157	161	23	90	0	0	0	6	0		80	0
484019d	Iqbal	0	26	78	1.62	0	0	0	0	410	0	0	1	220	172	32	134	1	5	0	5	0		160	0
436093d	Ramamoorthy	0	67	80	1.64	1	1	1	3	240	1	1	1	217	73	45	153	1	5	0	5	0		320	1
432233d	Jaganathan	0	37	68	1.65	0	1	1	2	540	0	0	1	171	230	38	100	1	5	0	5	0		320	0
616346d	Annamalai	0	60	71	1.72	1	0	0	1	240	0	0	0	150	77	26	101	2	5	0	5	0		640	0
432185d	Nagarajan	0	55	50	1.65	0	1	0	1	660	0	0	0	193	118	40	124	1	5	0	5	0		0	0
432352d	Kamalanathan	0	44	68	1.58	0	1	0	1	420	0	0	1	243	150	38	173	1	5	0	5	0		80	0
436106d	Kesavel	0	65	76	1.68	0	1	0	1	660	1	0	1	272	106	41	212	1	5	0	5	0		40	0
439184d	Shyed Naseer	0	46	65	1.68	1	1	1	3	240	0	1	1	157	265	26	87	1	5	0		1	0	0	0
295455d	Damodaran	0	46	66	1.68	1	0	0	1	540	0	1	1	201	249	31	137	0	5	0	5	0		640	0
439173d	Sampath	0	44	75	1.63	1	1	1	3	300	0	0	1	200	117	35	135	2	5	0	5	0		80	0
419162d	Arumugam	0	55	59	1.65	0	0	0	0	240	0	1	1	182	166	35	112	1	5	0		1	0	2560	1
420877d	Rajendran	0	47	74	1.74	1	1	1	3	420	1	0	1	256	246	38	168	1	5	0	5	0		320	0
757968c	Illal	1	43	65	1.66	1	1	0	2	300	0	1	0	166	94	29	99		5	0	5	0		320	0
425404d	Devaraj	0	52	70	1.65	1	1	1	3	180	0	0	1	238	322	34	164	0	5	0	5	0		320	1
428007d	Venkatachalam	0	62	72	1.7	1	1	0	2	240	1	0	1	126	280	22	60	1	5	2	5	0		320	1
469566d	Dayalan	0	50	70	1.66	1	1	0	2	225	1	1	0	245	196	39	167	1	5	0	5	0		320	1
469053d	Raji	0	37	64	1.58	1	1	0	2	300	0	0	1	142	109	35	72	0	5	0	6	0		80	0
432098d	Murali	0	51	72	1.64	0	0	1	1	480	0	1	0	153	75	28	105	1	5	0		1	2	0	0

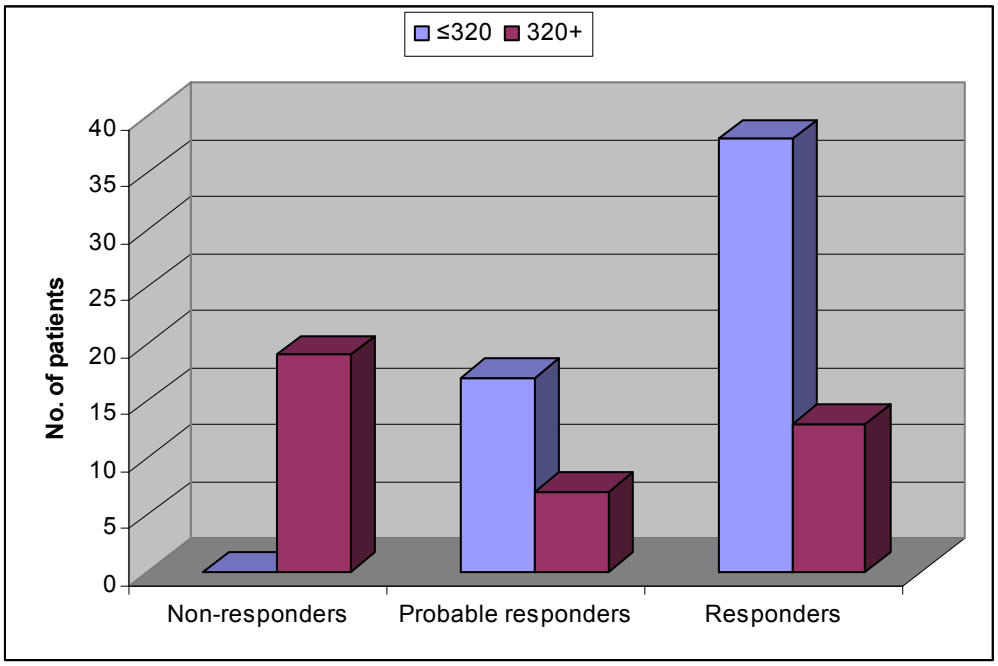
429004d	Murugesan	0	60	68	1.54	1	1	1	3	240	1	1	1	177	105	25	128	1	5	2	5	0		80	0
757536a	Selva Arasu	0	42	69	1.65	1	1	1	3	420	0	0	0	329	85	38	238	1	5	0	5	0		0	0
429075d	Venkatachalam	0	55	62	1.6	1	1	0	2	180	0	0	0	199	209	30	124	1	5	2	5	0		320	1
482884d	Sagadevan	0	62	64	1.68	1	1	1	3	120	1	0	0	198	93	36	123	1	5	0	5	0		40	1
465650d	Radhakrishnan	0	56	66	1.66	1	1	0	2	360	1	0	1	185	268	32	118	1	5	2	6	0		320	0
472172d	Arunagiri	0	65	64	1.6	1	1	1	3	170	0	0	0	149	82	29	93	1	5	0	5	0		80	1
483114d	Muthukrishnan	0	65	78	1.62	1	1	1	3	300	0	1	0	164	274	31	82	1	5	0		1	0	0	0
493531d	Dakshinamoorthy	0	63	68	1.58	1	1	1	3	120	0	0	0	187	99	44	111	1	5	0	5	0		80	1
004300d	Sundaramoorthy	0	55	70	1.68	1	1	0	2	240	1	0	0	219	119	44	138	0	5	0		1	2	0	0
608096d	Kanagaraj	0	49	62	1.7	1	0	0	1	300	0	0	1	185	106	42	117	1	5	0		1	2	1280	0
615789d	Kanniyan	0	59	64	1.64	1	0	0	1	300	1	1	0	181	262	27	103	0	5	0	5	0		1280	0
508461d	Ekambaram	0	60	65	1.68	1	1	1	3	230	0	1	1	188	74	32	143	0	5	0	5	0		80	1
518620d	Syed Farook	0	49	68	1.59	1	1	1	3	300	0	1	1	183	115	38	108	1	5	0	5	0		320	0
526113d	Shankar	0	42	71	1.69	0	0	0	0	360	1	1	1	193	394	20	104	1	5	0	5	0		1280	0
289227c	Julius	0	49	50	1.55	1	1	0	2	230	1	0	1	184	121	47	108	1	5	0	5	0		320	1
526258d	Dasarathan	0	56	76	1.71	1	1	1	3	170	0	1	1	159	208	25	91	1	5	0	5	0		640	1
530059d	Elavazhagan	0	45	58	1.54	1	0	0	1	300	1	0	1	245	428	30	132	0	5	0	5	0		640	0
530321d	Kandasamy	0	47	64	1.66	1	1	0	2	300	0	0	1	173	182	37	101	1	5	0	5	0		160	0
530402d	Muthukuruppan	0	59	63	1.64	1	1	1	3	180	0	0	1	172	96	34	100	1	5	0	5	0		320	1
533115d	Venugopal	0	48	70	1.73	1	1	1	3	180	0	1	1	196	77	35	125	0	5	0	5	0		640	1
535438d	Sasikala	1	37	62	1.51	1	1	1	3	660	0	0	0	200	109	45	123	1	5	0	5	0		0	0
535445d	Mariamma	1	56	68	1.58	1	1	0	2	530	1	0	0	148	90	49	78	0	5	0	5	0		0	0
540051d	Abdul Basheer	0	58	68	1.59	0	0	0	0	660	1	1	0	169	127	37	101	0	5	0		1	0	1280	0
591412d	Perumal	0	55	77	1.79	1	1	1	3	230	0	1	0	154	113	46	81	0	5	0	5	0		640	1
591698d	Jeyakumari (F)	1	60	62	1.54	1	1	1	3	30	1	0	0	153	38	51	83	0	5	0		1	2	320	1
601180d	Boopalan Kg	0	67	59	1.64	0	0	0	0	480	1	0	0	226	130	35	136	1	5	0	5	0		640	0
602217d	Nandagopal	0	52	80	1.66	0	1	1	2	660	1	1	1	143	129	39	78	0	5	0		1	2	640	0
554238d	Arumugam	0	44	64	1.71	1	1	1	3	240	0	0	1	207	135	40	135	0	5	0	5	0		0	1
582097d	Gowthaman	0	48	75	1.68	1	1	1	3	720	0	0	1	253	261	42	180	1	5	1	5	0		80	0
582064d	Loganathan	0	54	55	1.68	1	1	0	2	420	0	0	1	98	65	22	58	0	1	0	1	0		80	0
850868C	Narayanaswamy	0	46	59	1.62	1	1	1	3	420	0	1	1	170	120	35	97	0	5	0	5	0		0	0
582095d	Manivelan	0	44	60	1.65	1	1	0	2	720	0	0	1	217	132	43	143	1	5	0	5	0		320	0

563649d	Saravanan	0	36	72	1.69	1	1	1	3	300	1	0	1	111	101	23	67	0	5	0	5	0		640	0
577369d	Shameem	1	60	63	1.54	1	1	1	3	180	1	1	0	162	82	31	112	1	5	0	5	0		1280	1
577200d	Lakshmanan	0	59	75	1.6	0	0	0	0	590	1	0	0	156	104	29	91	0	5	0	5	0		1280	0
577179d	Abdul Khader	0	64	75	1.68	0	0	0	0	540	1	1	0	206	133	30	145	1	5	0	5	0		0	0
577154d	Babu s m	0	55	77	1.55	1	1	1	3	170	1	0	0	136	149	25	79	0	5	0	5	0		1280	1
577131d	Abdul Majid	0	69	52	1.56	1	1	0	2	180	1	1	1	139	73	55	64	0	5	0	5	0		0	0
616228d	Mohan	0	61	56	1.61	1	1	1	3	330	0	1	0	141	91	39	81	1	5	0	5	0		0	0
577459d	Duraiswamy	0	50	62	1.64	1	1	1	3	180	0	0	1	284	175	28	192	0	15	0	15	0		1280	1
577430d	Radhakrishnan	0	55	78	1.72	1	1	1	3	110	0	0	1	175	122	26	105	0	5	0	5	0		0	1
613108d	Sampath	0	45	74	1.71	1	0	0	1	480	0	0	1	103	60	34	55	0	5	0	5	0		2560	0
577438d	Gopal	0	45	74	1.68	1	0	0	1	420	0	0	0	152	232	29	81	1	5	0	5	0		1280	0
511154d	Balakrishnan	0	60	63	1.55	0	1	0	1	720	0	1	0	141	94	28	83	1	5	0	5	0		80	0
508443d	Shanmuganathan	0	28	69	1.59	0	1	0	1	290	0	0	1	183	132	36	118	1	5	0	5	0		640	0
526345d	Lakshmi k c	1	56	64	1.71	1	1	1	3	270	0	0	0	223	146	49	129	0	5	0	5	0		40	0
831592a	Vasanthan	0	62	73	1.7	1	1	1	3	240	1	1	1	156	100	32	89	0	5	0	5	0		320	1
577024d	Srinivasan	0	50	89	1.7	0	0	0	0	720	0	0	0	195	349	37	108	0	5	0	5	0		1280	0
572465d	Saleem Ahmed	0	42	76	1.68	1	1	1	3	420	0	0	1	171	84	32	114	1	5	0	5	0		40	0
541705d	Amavasaikannu	0	50	48	1.6	1	1	1	3	290	0	0	1	145	103	44	69	1	5	0	5	0		80	0
540204d	Dharani S	0	47	62	1.58	1	1	0	2	180	0	1	0	193	142	33	121	0	5	0		1	3	2560	1
549189d	Narasimhan P	0	50	54	1.58	1	1	1	3	300	0	0	0	167	178	38	93	1	5	0		1	2	160	0
540266d	Munaf	0	61	76	1.68	1	1	1	3	660	0	0	1	223	117	35	148	0	5	0	5	0		160	0
544573d	Sekaran	0	65	50	1.56	1	1	1	3	120	1	0	0	198	102	44	119	1	5	0	5	0		1280	1
549101d	Muneer ahmed	0	52	62	1.58	0	0	1	1	660	1	0	0	185	140	45	109	1	5	0		1	2	80	0
339805c	Mohan	0	40	83	1.7	1	1	1	3	470	0	0	1	253	141	34	179	1	5	0	5	0		640	0
561521d	Anwara Begum	1	48	58	1.54	0	1	0	1	540	1	0	0	318	1138	53	119	1	5	0	5			1280	0
734160c	Geeta	1	45	93	1.61	1	1	1	3	120	1	0	0	142	136	31	77	0	5	0	5	0		320	0
864517d	Anand sedan	0	63	68	1.68	1	0	0	1	660	1	0	1	199	101	41	141	0	5	0	5	0		40	0
544139d	Murali	0	37	68	1.71	0	1	0	1	300	0	0	1	167	163	25	94	0	5	0	5	0		5120	0
554280d	Chitti babu	0	48	69	1.69	1	0	0	1	300	0	0	0	75	99	24	41	1	5	0	5	0		2560	0
580631d	Saravanan	0	39	66	1.69	1	1	1	3	110	0	0	1	227	216	44	136	1	5	0	5	0		40	1
572079d	Prabhu	0	47	73	1.68	1	0	1	2	170	0	1	0	223	219	27	145	1	5	0		1	1	1280	1
572028d	Md Ali	0	50	90	1.63	0	0	0	0	600	1	1	1	188	156	27	126	1	5	0	5	1	3	2560	0

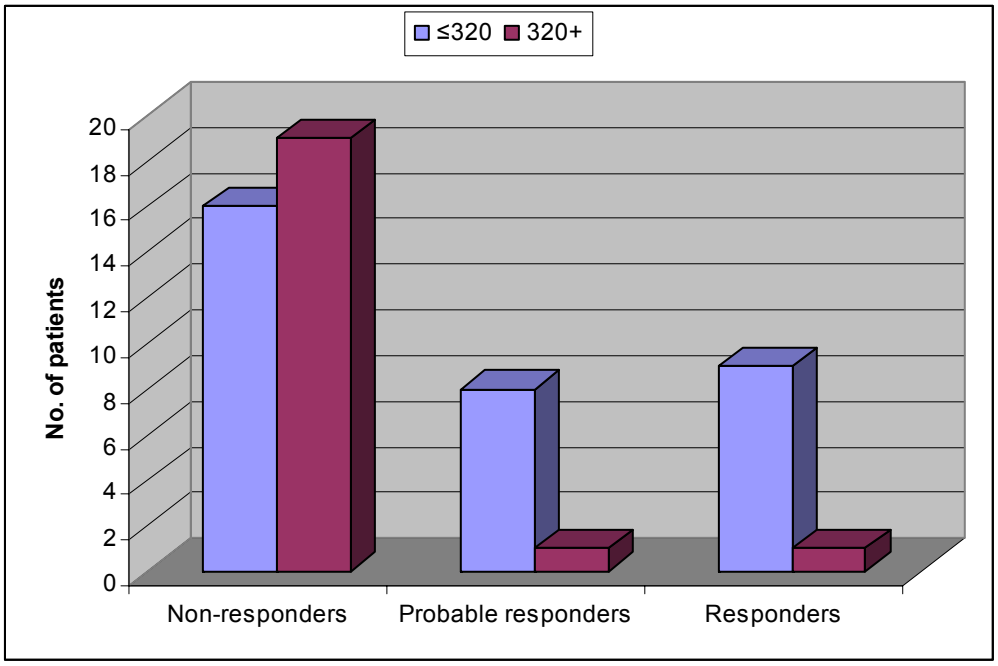
591215d	Vilvanathan	0	62	68	1.69	0	0	0	0	530	0	0	0	106	56	63	37	1	5	1		1	3	320	0
597371d	Thambi Durai	0	58	71	1.62	1	1	1	3	90	0	1	1	174	63	27	114	1	5	1	5	0		1280	1
603228d	Neethi Kumar	0	26	96	1.7	1	0	0	1	180	0	0	1	158	192	34	103	1	5	0	5	0		1280	0
449298d	Sadagopan K V	0	70	69	1.62	1	1	0	2	120	1	1	0	149	210	32	75	1	5	0	5	0		640	1
563569d	Prabhakaran	0	40	58	1.61	0	1	0	1	600	1	0	1	183	165	34	111	1	5	0	5	0		0	0
023854d	Natarajan	0	56	66	1.7	0	0	0	0	300	0	0	1	116	80	28	69	0	5	0	5	0		2560	0
572170d	Sekar G	0	48	51	1.55	0	1	1	2	720	1	1	0	256	121	53	121	1	5	0	5	0		80	0
603264d	Kumar	0	38	57	1.56	1	1	1	3	180	0	0	1	219	157	37	127	0	5	0	5	0		1280	1
895316c	Samuel J	0	50	52	1.56	0	1	0	1	480	1	1	0	135	187	41	69	1	5	0		1	3	1280	0
518292d	Anandan Y	0	45	83	1.68	0	1	0	1	240	0	0	0	221	67	41	148	1	5	0	5	0		1280	1
609266d	Thangavel	0	66	60	1.62	0	1	0	1	270	1	0	1	148	68	45	78	0	5	0	5	0		640	0
608492d	Shivalingam	0	62	64	1.64	0	1	1	2	330	0	0	1	236	461	39	127	1	5	0	5	0		640	0
608541d	Kannaiyan	0	50	76	1.71	1	1	1	3	270	0	0	1	176	140	31	107	1	5	0	5	0		5120	0
557184d	Abdul Kudhoos	0	35	77	1.6	0	1	0	1	660	0	1	0	169	233	28	95	1	5	0	5	0		1280	0
591369d	Ilayarasan	0	34	76	1.68	1	1	1	3	60	0	0	0	148	309	24	66	2	1	0	1			0	1
577374d	Sampath	0	62	64	1.65	0	1	0	1	410	0	1	0	178	227	32	101	0	5	1	5	0		320	0
559234d	Namasivayam	0	43	63	1.6	1	0	0	1	360	1	0	1	161	102	25	100	0	5	0	5	0		1280	0
563554d	Rajamani	0	60	64	1.66	0	0	0	0	660	1	0	0	179	97	30	134	1	5	0	5	0		1280	0
562648d	Malay Acharya	0	49	51	161	1	1	0	2	120	1	1	0	251	350	44	140	0	5	0		1	1	320	0
570730d	Raman M	0	43	65	1.64	0	0	1	1	660	0	1	0	163	246	32	87	0	5	0		1	2	640	0
567175d	Samuel Victor	0	62	71	1.62	0	0	0	0	720	0	0	0	236	127	39	148	1	5	0	5	0		1280	0
607544d	Rafeeq Khan	0	50	70	1.68	1	1	0	2	240	1	1	1	148	122	32	100	0	5	0	5	0		320	1
549231d	Mohan Raj	0	38	78	1.7	1	1	1	3	60	0	0	1	187	173	35	114	1	5	0	5	0		320	1
514263d	Bairavan	0	46	65	1.58	0	1	0	1	465	0	0	1	230	56	40	151	0	5	0		1	2	2560	0
508359d	Joseph S	0	67	62	1.66	0	1	1	2	480	0	0	0	122	140	24	64	1	5	1	5	0		0	0
608552d	Thirunavukarasu	0	50	76	1.61	0	1	0	1	480	1	0	0	143	131	34	76	0	5	0	5	0		5120	0
588256d	Kumar L	0	55	65	1.6	1	1	0	2	270	0	0	1	158	147	41	82	1	5	1		1	0	640	0
582461d	Natesan	0	65	66	1.58	0	0	0	0	660	1	0	0	204	104	38	122	1	5	0	5	0		1280	0
582136d	Jeeva Amma (F)	1	51	60	1.55	1	1	1	3	210	0	0	0	274	201	41	172	0	5	0	5	0		160	1
424592d	Govindasamy	0	46	78	1.7	0	1	0	1	180	1	1	1	289	267	43	179	0	5	0		1	1	1280	1
475812c	Lakshmi (F)	1	56	52	1.48	1	1	0	2	240	1	1	0	274	770	25	137	0	5	0	5	0		320	0
591543d	Sai K	0	55	61	1.58	0	1	0	1	660	0	0	1	184	148	36	104	0	5	1	5	0		640	0

398746d	Dakshinamoorthy	0	61	68	1.68	1	1	0	2	180	0	1	0	133	190	32	69	1	5	0	5	0		10240	1
439158d	Ragunathan	0	42	60	1.6	1	1	1	3	300	0	0	1	195	124	28	133	1	5	0	5	0		160	0
432070d	Selvarajan	0	52	54	1.6	1	0	0	1	450	1	0	0	175	112	29	123	0	5	0		1	2	160	0
500508d	Soundarajan	0	45	66	1.68	1	1	1	3	240	1	1	1	233	697	29	94	1	5	2	5	0		160	0
505557d	Thanigaimalai	0	59	65	1.58	0	0	0	0	660	1	0	1	217	291	35	121	2	5	0		1	2	1280	0
572464d	Moorthy	0	45	47	1.55	1	1	0	2	240	0	0	1	109	59	30	59	0	0	0	0	0		0	0
577958d	Ramamoorthy	0	62	58	1.63	1	1	1	3	180	1	1	1	151	101	26	95	0	5	0	5	0		80	1
616197d	Vanaja	1	32	73	1.57	1	1	1	3	255	0	0	0	112	94	62	112	1	5	0	5	0		640	0
537687d	Debabrata	0	52	68	1.62	1	1	0	2	540	1	1	1	178	150	30	107	0	5	0		1	3	80	0
614050d	Srinivasan	0	36	72	1.68	1	1	0	2	210	0	0	1	185	258	45	100	1	5	0	5	0		320	1
075027c	Paramasivam	0	68	63	1.6	0	0	0	0	480	0	1	0					1	5	0		1	2	0	0
422167d	Deiva sigamani	0	70	68	1.58	1	1	1	3	270	1	0	1	130	158	21	75	0	5	2	5	0		0	0
432188d	Jebasingh	0	48	79	1.63	1	1	1	3	180	1	1	0	217	106	31	155	0	5	0	5	0		0	1
591218d	Subramani	0	68	51	1.56	1	1	1	3	410	0	0	0	191	474	28	74	1	5	1	5	0		80	0
745900b	Kannammal	1	65	78	1.56	1	1	1	3	300	1	1	0	128	86	31	71	1	5	0	5	0		160	0
535088d	Nagarajan	0	67	74	1.62	0	0	0	0	300	1	1	1	144	149	24	83	0	5	0	5	0		1280	0
449389b	Rajamanickam	0	47	68	1.64	0	0	0	0	300	0	1	0	159	79	37	105	1	5	0		1	2	640	0
630260d	Nithyanandam	0	53	72	1.75	1	1	1	3	420	0	0	1	208	129	41	137	1	5	0	5	0		80	0
630425d	Srinivasan	0	56	66	1.65	1	1	1	3	270	1	0	1	179	164	20	118	1	5	0	5	0		80	0
638125d	Gopal	0	69	58	1.63	1	1	1	3	330	0	0	1	256	126	37	179	1	5	0	5	0		640	0
630499d	Dasthagir	0	42	74	1.7	1	0	0	1	360	1	0	0	109	192	30	51	1	5	0		1	2	2560	0

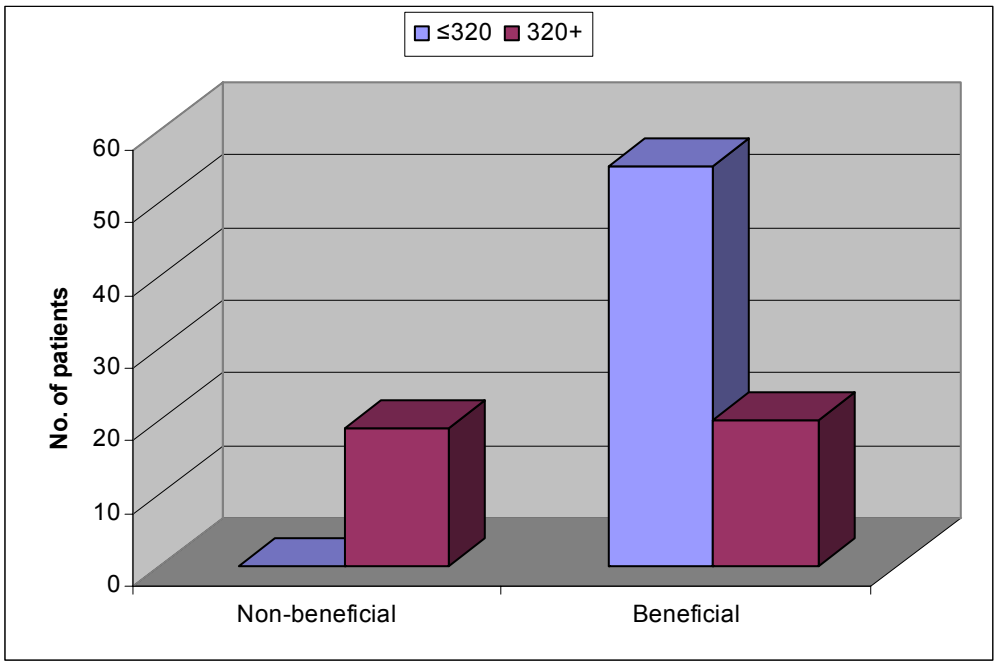
Response to thrombolysis in patients presenting with window period ≤6 hours (Table 23)



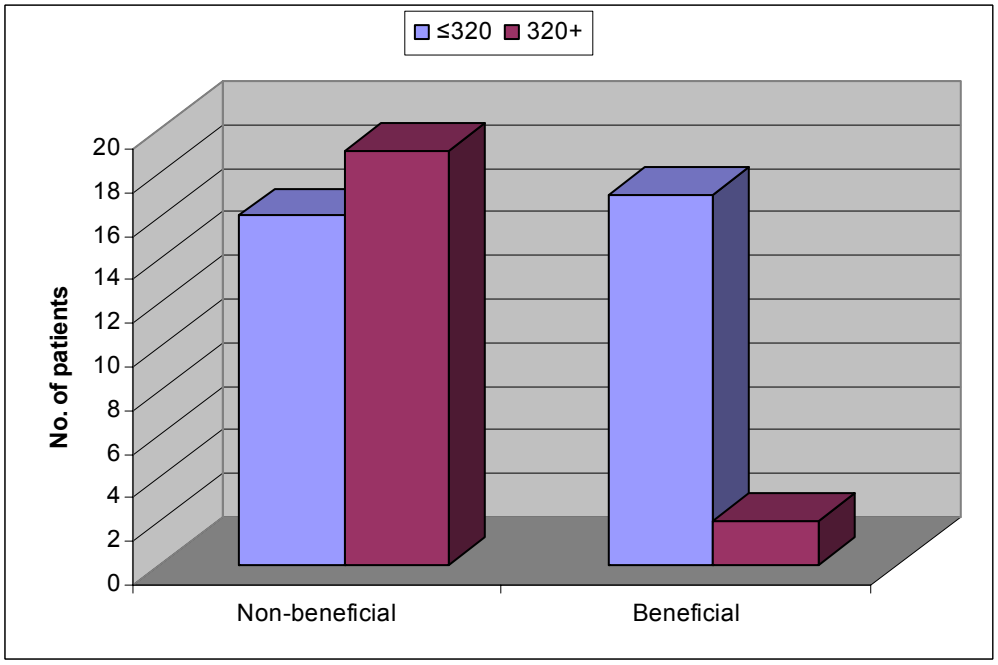
Response to thrombolysis in patients presenting with window period >6 hours (Table 24)



Benefit of thrombolysis in patients with window period less than 6 hours (Table 25)



Benefit of thrombolysis in patients with window period more than 6 hours (Table 26)



MACE in patients in relation to the antistreptokinase antibody titres (Table 33)